A GUIDE TO ALZHEIMER'S SCIENCE

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This guide presents basic information about the science and medicine of Alzheimer's disease. It explains the behavioral and biological pathology seen in Alzheimer's, genetic and other risk factors for the disease, the process of diagnosing Alzheimer's, its stages and symptoms, and treatment for Alzheimer's. It briefly describes the stresses experienced by family caregivers of Alzheimer's patients and some of the coping mechanisms successful caregivers use. It was written to give leaders of the Alzheimer's support group at the University of Houston Counseling Center an overview of essential topics and issues of concern to Alzheimer's group members.

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disease that causes a progressive and irreversible dementia, or general decline in cognitive abilities, and is the commonest cause of dementia in the elderly. The prevalence of AD worldwide ranges from about 2% at age 70–74 to 32% at age 90–94. The cognitive and behavioral symptoms of AD begin with memory impairment for recent events and progress to a severe and disabling cognitive decline and eventually to death over an average period of 10 years. Major AD symptoms appear in the same order in all AD patients, which is the principal basis for its diagnosis. Memory impairment is followed by language and visuospatial impairments, by impairments in executive functioning (planning, reasoning, and judgement), and finally by impairments in motor skills and changes in personality. Neurologic disease in AD also spreads from region to region of the brain in a predictable pattern. Neuropathology in AD consists mainly of amyloid plaques, neurofibrillary tangles, and brain atrophy. Amyloid plaques are masses of starchlike (amyloid) protein that form outside neurons and cause a cascade of biological reactions that degrade and destroy neurons. Neurofibrillary tangles are paired helical filaments of tau protein that form within neurons and that are also neurotoxic. Atrophy, the loss of brain mass, results as neurons die.

AD can be divided into three categories based on the genetic mechanisms of each. People with Down syndrome invariably develop AD neuropathology after age 40. However, all other people with AD have either familial AD (25%) or nonfamilial AD (75%). Familial AD consists of late-onset familial AD, which is more common and occurs at age 65 or older, and early-onset

familial AD, which comprises less than 2% of all AD cases and occurs before age 65. Nonfamilial AD is diagnosed if no AD has occurred in the last 3 generations of the AD patient's family. Early-onset familial AD is inherited in an autosomal dominant manner: anyone who inherits one copy of a defective gene, of which three have been identified, invariably manifests AD at an age typical for the mutation. Late-onset familial AD involves multiple susceptibility genes that only predispose people to getting AD, and only one of these genes, the apolipoprotein E (APOE) gene has been identified. One's risk of developing late onset familial AD is determined by which 2 of 3 different APOE alleles (ε2, ε3, or ε4) one inherits. The percentage of white Americans over 60 with AD varies with allele combination, from 2% (ε2/ε2) to 70% (ε4/ε4), the average rate for all allele combinations being 8.7%. One's cumulative lifetime risk of developing nonfamilial, or sporadic AD is about 10%.

In addition to genetic complement, there are three other nonmodifiable risk factors for AD: AD risk is strongly correlated with age and weakly correlated with sex and ethnicity. Likely modifiable risk factors for AD include diet, cardiovascular health, alcohol consumption, exercise, educational attainment, and head injury—although these factors have only a marginal influence on risk relative to the risk conferred by age and genotype. Little support exists for believing psychological stress, hormone levels, environmental toxins including metals, or the use of nonsteroidal anti-inflammatory drugs are risk factors for AD.

No laboratory test exists for AD. Therefore, the diagnosis of AD is made when a patient has a pattern of symptom development characteristic of AD and when all other causes of dementia have been ruled out. Clinical diagnosis of this kind is 85–90% accurate, as verified by

autopsy, when performed by clinicians experienced in diagnosing dementia. A comprehensive dementia examination consists of a history-taking; a physical evaluation, including assessment of cognitive abilities; and laboratory tests. Genetic testing, which only slightly improves diagnostic accuracy, is not considered useful in routine evaluations. To diagnose AD, the clinician must rule out many systemic diseases that cause dementia symptoms, such as severe vitamin B_{12} deficiency, as well as other major neurodegenerative diseases, such as frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt–Jacob disease, vascular dementia, and normal pressure hydrocephalus, all of which cause dementia. Depression and delirium—an acute, fluctuating condition with sudden onset—must also be ruled out. Criteria for diagnosing dementia and AD are published by the American Psychiatric Association and the National Institute of Neurologic and Communicable Diseases–Alzheimer's Disease and Related Disorders Association. In the US, primary-care physicians often make an initial assessment of possible dementia but normally refer patients to a specialist, a neurologist or geriatric psychiatrist, for diagnosis.

The most commonly used system of describing the stages of AD labels these mild, moderate, or severe, depending on whether the patient can live without assistance, requires assistance with daily activities, or requires nursing home care. Symptoms of AD vary by stage and are both cognitive and noncognitive (psychiatric or behavioral). Common cognitive symptoms include impairments of executive functioning; memory and orientation; motor functions; abstract thinking; language; learned movement; and recognition of people and objects. Noncognitive symptoms include depression; other disorders of mood; delusions and hallucinations; apathy; anxiety; agitation; disinhibition; purposeless activity; sleep disorders;

aggression and inappropriate sexual behavior; and delirium. The sole initial symptom of AD, however, is mild impairment of memory for recent events.

Only two classes of drugs have been approved by the Food and Drug Administration for the treatment of the cognitive symptoms of AD. Acetylcholinesterase inhibitors, such as rivastigmine (Excelon), increase the amount of the neurotransmitter acetylcholine active at synapses and compensate for the loss of acetylcholinergic neurons in AD. The glutamate receptor blockers—of which only one drug, memantine (Namenda), has been approved—reduce the toxicity of the neurotransmitter glutamate, which is released by damaged neurons and which at high concentrations is neurotoxic. These two classes of drugs make marginal but clinically significant improvements in cognitive functioning and in some noncognitive symptoms. For example, use of these drugs can postpone nursing home placement by up to two years. Experts recommend that a medication from one or both of these classes be routinely started with all AD patients at the time of diagnosis and continued throughout all but the end stage. Of all alternative treatments for the cognitive symptoms of AD, evidence of efficacy exists only for vitamin E, for possibly slowing the progression of AD. Vitamin E in recommended doses also causes few, if any, side effects. Many medications are used to treat the noncognitive symptoms of AD, with specific medications being chosen for their efficacy in treating specific symptoms, for their side effects, and for their tolerability by dementia patients.

Nonpharmacologic interventions often improve cognitive or noncognitive symptoms of AD. Cognitive functioning improves with graded assistance (least assistance needed) combined with practice and positive reinforcement in everyday tasks. “Global stimulation,” such as rec-

reational activity, participation in hobbies, exercise, and social interaction, also has a positive effect on cognitive functioning. Common-sense nonpharmacologic interventions should always be considered first for treating noncognitive symptoms. These practical strategies usually involve identifying the causes of behavioral problems. For example, established nonpharmacologic regimens are effective for improving the sleep of AD patients and for reducing the risk and severity of delirium.

Finally, intensive, long-term education, support, and counseling for family caregivers significantly improves their ability to manage the symptoms of AD and enhances the quality of life of their loved ones. Education, support, and training for family caregivers reduces the depression, tension, anger, fatigue, and confusion they often experience and, like medication for AD, can significantly delay nursing home placement.

A GUIDE TO ALZHEIMER'S SCIENCE

I. INTRODUCTION

This guide presents basic medical and scientific information needed to understand Alzheimer's Disease (AD). It was written to help prepare doctoral interns and undergraduate psychology majors for their internship or practicum assignments as group leaders of the Alzheimer's caregiver support group run by the Counseling Center at the University of Houston (UH). At UH, internship and practicum supervisors teach the theory and technique of group counseling and group leadership to the Alzheimer's group leaders. This guide is meant to supplement that core training in counseling by reviewing current scientific knowledge about AD. An understanding of AD from a biological and behavioral standpoint, including an understanding of the causes, diagnosis, treatment, and course of AD, is essential for answering Alzheimer's group member questions, understanding their concerns, and empathizing with their experiences. This guide, written to fulfill a Counseling Center internship project requirement in the spring of 2006, summarizes current research findings about these scientific topics and presents findings much the way psychology texts do, by discussing outcomes of significant studies that are cited at the end of the guide.

AD is a disease of the brain that causes a progressive decline in intellectual abilities and that accounts for 60% to 70% of cognitive impairment in the elderly [12:2335]. An estimated 5 million Americans suffer from AD, only half of whom have been diagnosed [16:xi], and treatment for AD in the US costs nearly $100 billion a year in direct and indirect costs—more per

patient than any other disease of the elderly [27:11]. Nursing home care costs alone average $47,000 per patient per year [12:2335]. By 2050, unless a way to prevent AD is found, the number of US cases will be approximately 14 million [16:xi].

This guide presents essential information about the biology, symptoms, and treatment of AD. It has five major sections: fundamental biological and behavioral changes seen in AD; risk factors for developing AD; the diagnosing of AD; stages and symptoms of AD; and treatment of AD. A conclusion briefly discusses family caregiver stresses and coping strategies. The guide was written so that advanced undergraduates in psychology can understand the concepts presented in the text.

II. DEFINITION OF ALZHEIMER'S DISEASE

AD is a progressive degenerative disease of the brain. AD causes a dementia, or general decline in cognitive functioning, with characteristic cognitive symptoms, behavioral symptoms, and cellular pathology in the brain.

Alzheimer's Disease as a Dementia

AD is a progressive neurologic disorder that causes dementia. T.J.Grabowski and A.R. Damasio define dementia in broad conceptual terms as an "acquired and persistent impairment of intellectual faculties, affecting several cognitive domains, that is sufficiently severe to impair competence in daily living, occupation, or social interaction" [28:2]. Thus, dementia is a decline from a previous level of intellectual functioning that does not fluctuate over time. In addition, dementia is not a decline in an isolated intellectual ability but instead involves deterioration in "several cognitive domains." For example, a marked decline in language skill alone is an aphasia, not a dementia, since aphasia does not involve a general deterioration of mental functioning. Most, but not all dementias are progressive (some are static and a few are reversible) and many, but not all dementias involve impairment of memory. Various practice guidelines for assessing dementia specify the number and nature of the cognitive impairments required for the diagnosis of dementia. AD, which is always progressive, is the commonest cause of dementia, but there are others, such as frontotemporal dementia, dementia with Lewy bodies, vascular dementia, normal pressure hydrocephalus, and Creutzfeldt–Jakob disease. Specific criteria for the diagnosis of dementia and AD are discussed in the chapter "Diagnos-

ing Alzheimer’s Disease" under “Differential Diagnosis” on page 40. This section also describes the main clinical features of the other common dementias.

Cognitive and Behavioral Changes

AD is distinguished from other dementias by its cognitive and behavioral symptoms and by the characteristic order in which they appear [28:4–5; 30:692; 68]:

1. Invariably, the first symptom to appear is a slow but persistent decline in one’s ability to remember recent events, a forgetfulness known as anterograde amnesia. This early memory impairment may be the only symptom of AD at this stage. However, it can be accompanied by subtle changes in mood and personality, such as irritability, anxiety, apathy, or indifference.

2. Deficits in language (such as impaired word-finding ability), in simple math skills, in visuospatial ability (such as the inability to draw a simple design), and in spatial orientation (such as difficulty finding one’s way around familiar surroundings) develop next. Judgement and social and interpersonal skills likely remain normal at this stage.

3. A more general decline in cognitive ability follows, involving frequent, conspicuous memory lapses and obvious problems with planning, reasoning, and judgement that make the patient partially dependent on others for assistance. This mild dementia progressively worsens until the patient becomes fully dependent on caregivers for assistance with even the most basic activities of daily living.

4. Typically, major personality changes and psychiatric symptoms such as agitation or psychoses, appear only in the later stages of AD, while deficits in motor skills, which directly interfere with activities such as walking, eating, bathing, and grooming, appear only in the final stages of the disease. AD patients who survive the full course of the disease will lose virtually all language and motor skills and the ability to walk, sit up, smile, or hold their heads up. Signs of severe neurologic impairment, such as seizures, muscle rigidity, abnormal reflexes, and difficulty swallowing occur at the end. The most common cause of death in end-stage AD is aspiration pneumonia caused by difficulty swallowing and breathing and the use of feeding and respiration tubes [34].

Thus, progressive memory impairment, which worsens throughout the course of AD, precedes other symptoms of AD and is followed by general cognitive decline in which deficits in language, visuospatial skills, and spatial orientation occur early followed by obvious problems with abstract thinking, planning, and judgement. Decline in social skills and major personality change occur late in AD, and impairment to motor and sensory abilities develops only in the final stages. This pattern of symptom development, which on average ensues over a decade from diagnosis to death (with a range of 3–20 years) [68], distinguishes AD from other forms of dementia. Various systems for dividing symptom development in AD into stages have been devised, and these are discussed in the chapter “Stages and Symptoms of Alzheimer’s Disease” on page 52.

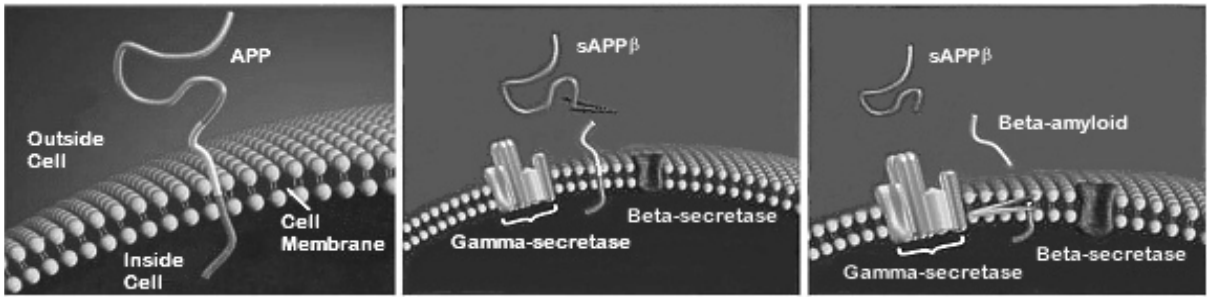
Biological Changes

The cognitive and behavioral symptoms of AD result from abnormalities in the brains of people with AD, and these brain pathologies also distinguish AD from other dementias. The three hallmarks of AD neuropathology are amyloid plaques, neurofibrillary tangles, and brain atrophy [16:73–80; 27:11; 30:692]. This AD pathology spreads from region to region of the brain in a more or less predictable pattern.

Amyloid plaques (also called senile plaques or neuritic plaques) are spherical masses, usually many times larger than individual neurons, that form between and around neurons. An amyloid plaque consists of a core of starchlike (amyloid) protein surrounded by misshapen neurons, small fibrils of amyloid, and debris from degenerating neurons [56:1222]. Neurofibrillary tangles are twisted filaments of protein with a paired helical structure that form inside neurons. Amyloid plaques and neurofibrillary tangles destroy synapses [56:1223] (the connecting points between neurons) and neurons, and brain atrophy, the visible shrinking of areas of the brain, results. Further, the appearance of amyloid plaques, neurofibrillary tangles, and brain atrophy in different functional regions of the brain follows a pattern that is characteristic of AD and corresponds to the order in which the major symptoms of AD appear [9:III/18–III/19; 30:692–693]. Amyloid plaques and neurofibrillary tangles do not have identical patterns of distribution in the brain, however. Cognitive decline, atrophy, and the behavioral symptoms of AD all correlate better with the progression of neurofibrillary tangles from region to region in the brain than with the appearance of amyloid plaques [16:79; 17; 56:1223].

Amyloid plaques. Much is known about the chemistry of plaque formation [16:73–80; 27; 56]. The cores of amyloid plaques are formed from protein fragments (peptides), known as β-amyloid (Aβ) peptides, that have been detached from larger proteins, called amyloid precursor proteins (APPs), found in cells throughout the body. APPs, which are chains of 770 amino acids (the building blocks of peptides and proteins), are produced inside neurons and transported to their cell membranes where they become lodged, part of the molecules extending inside the cell and part extending outside. An enzyme called β-secretase, attached to the outer surface of the cell membrane, cuts the APP molecule near the surface, releasing a large segment of APP (called secreted derivative APP, or sAPPβ) into the aqueous environment outside the cell. Although the biological function of this segment is not well understood, it does not contribute to Alzheimer's pathology. The stumps of APP protruding from the cell membrane are cut within the membrane by the enzyme γ-secretase, and the resulting short fragments of APP are also released outside the cell. These fragments are of various lengths, but commonly they are either 40 or 42 amino acids long and called amyloid beta 40 (Aβ40) peptides or amyloid beta 42 (Aβ42) peptides. Aβ42 peptides, but not Aβ40 and shorter peptides, tend to stick together, forming short chains, or oligomers, and the oligomers in turn stick together forming tiny fibrils. These fibrils clump together to form the cores of amyloid plaques. Similar fibrils are found within the walls of small arteries in the cortex of the brain, where they may cause small infarcts (blockages) or hemorrhages [14:197]. Figure II-1 illustrates how β-secretase and γ-secretase split APP molecules, producing an Aβ peptides.

A large body of evidence suggests that amyloid plaques—or the peptides or oligomers that form them—cause the degeneration and eventual loss of neurons in AD, although the exact



a. b. c.

Figure II-1: Production of Aβ peptides at the cell membrane. (a) APP molecule lodged in the cell membrane. (b) β-secretase cuts APP outside the cell membrane. (c) γ-sectretase splits APP within the cell membrane, releasing an Aβ peptide outside the neuron [53].

processes by which this occurs are not clear [27:11–13; 69]. For example, research suggests Aβ oligomers can attach directly to synapses, disabling them [41]. Further, Aβ deposits outside neurons may stimulate the development of neurofibrillary tangles within neurons through complex processes initiated by Aβ-induced inflammation [3; 56]. Other mechanisms of Aβ toxicity are being investigated as well. This theory of AD, in which amyloid deposits initiate neuron degeneration that occurs through multiple processes, is called the amyloid-cascade hypothesis. Current scientific evidence tends to support the amyloid-cascade hypothesis over competing theories [69].

Neurofibrillary tangles. The second pathologic process characteristic of AD is the formation of neurofibrillary tangles within the cell bodies of neurons. Neurofibrillary tangles are paired helical filaments of tau protein. Tau protein is normally attached to microtubules in neurons, which transport substances along the lengths of neurons and give them structural support. In AD, overactive enzymes, called kinases, hyperphosphorylate tau by adding extra phosphate groups to the protein. In turn, tau proteins detach from the microtubules and stick together,

forming paired helical filaments. Similar hyperphosphorylated filaments appear in the axons and dendrites of neurons, the long processes that branch away for the cell body. These misshapened axons and dendrites, called neuropil threads, are commonly found within amyloid plaques. Neurons filled with neurofibrillary tangles and similar filaments become dysfunctional and eventually die. In addition, neurofibrillary change in neurons is closely correlated with loss of synapses, which precedes other forms of neuron degeneration [56:1223].

Finally, damaged neurons, Aβ deposits, and neurofibrillary tangles activate chronic inflammation around diseased areas, initiating many reactions, some of which further damage or destroy neurons. This localized inflammation is considered a significant factor, along with the formation of amyloid plaques and neurofibrillary tangles, in AD pathology [3]. Thus, the loss of neurons in AD happens through multiple, complex processes. However, the presence of amyloid plaques and neurofibrillary tangles of sufficient density in specific areas of the brain found at autopsy in patients who displayed the behavioral signs of Alzheimer's dementia are the necessary and sufficient findings for diagnosing AD with certainty in clinical practice [50]. Mechanisms causing the initial increase in Aβ production and neurofibrillary tangle formation in AD are poorly understood. However, evidence suggests that multiple genetic factors, physiological damage to brain tissue, and processes of normal aging interact to produce Alzheimer's degeneration [7], although a few rare types of AD are known to be caused directly by specific gene mutations. These factors are discussed in the chapter "Causes of Alzheimer's Disease" on page 12.

Spread of AD pathology. The appearance of neurofibrillary tangles in different regions of the brain follows a remarkably consistent pattern with few individual differences [9; 17]. Some researchers have noted that neurofibrillary tangles appear to spread through the brain primarily in areas with an abundance of "long, sparsely myelinated or unmyelinated" axons and axons myelinated late in individual development [9:III19–III21]. Axons are the single, long extensions of nerve cells that conduct nerve impulses away from the cell body, and myelin is a coating of alternating layers of lipids and proteins wrapped around axons by accessory cells that serves as a kind of insulation and increases the rate at which neurons conduct impulses [61:15]. Neurofibrillary tangles first appear in the transentorhinal and entorhinal cortices, which form a small region of cerebral cortex in the temporal lobe of the brain. This entorhinal area conveys information from other cortical areas to the hippocampus, a structure within the temporal lobe essential for the formation of new memories. Areas of the entorhinal cortex are also essential to maintaining one's sense of spatial orientation (knowing one's location, distance, direction) [31]. Figure II-2 illustrates how AD pathology spreads through the major lobes of the brain.

As AD progresses, neurofibrillary tangles spread through the hippocampus and the temporal lobe, and patients may begin to show signs of memory impairment, primarily forgetfulness associated with new learning (memory for recent events), and spatial disorientation (getting lost in familiar surroundings). Neurofibrillary tangles appear sequentially in other areas of the cerebral cortex. Areas responsible for language and visuospatial abilities (such as drawing a simple design) are compromised next, as are cortical association areas, regions that interconnect major functional areas of the brain and that are essential for higher cognitive functioning.

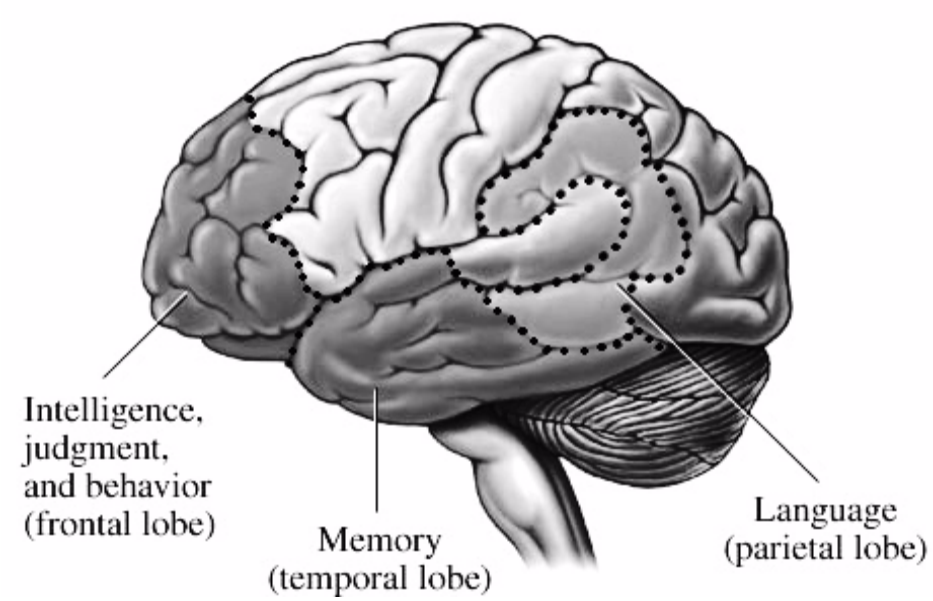


Figure II-2: Spread of AD pathology through the brain. Neurofibrillary tangles first appear in the temporal lobe and then spread to the parietal lobe, the frontal lobe, and the rest of the brain [57].

Patients may exhibit language and visuospatial deficits at this stage along with the first signs of general mental deterioration and subtle personality change. Widespread devastation of the cortex follows. Dementia is then obvious, and the diagnosis of AD by a physician is usually made. In the final stages of AD, remaining areas of the cortex that have thus far been spared, areas responsible for motor, sensory, and visual abilities, develop neurofibrillary disease, as do specific subcortical areas. Areas of the brain that typically sustain less damage from neurofibrillary tangles include the motor system, the acoustic system (responsible for hearing), and the occipital region (responsible for vision), although eventually even these areas deteriorate. In the final stages of AD, most areas of the brain are visibly atrophied, and the brain weighs markedly less. Patients are severely demented and show major disturbances of autonomic functions that reflect degeneration of subcortical structures.

III. CAUSES OF ALZHEIMER'S DISEASE

While much about AD neuropathology remains unclear, researchers have discovered that certain risk factors—genetic, medical, lifestyle, and environmental conditions—are associated with an increased likelihood of developing AD.

Genetic Findings

Because the biology of AD is not fully understood, the exact cause of AD in most cases is uncertain. However, researchers have established that certain risk factors—specific genetic, medical, and environmental conditions—are associated with the development of AD. Inherited genetic mutations, for example, are known to cause a few extremely rare forms of AD in all individuals possessing the defective genes. Otherwise, possession of defective genes only increases the probability that an individual will get AD, and in most cases of AD (about 75%), specific genetic influences, although they likely exist, have yet to be identified. Epidemiological studies suggest that genetic factors play a large role in causing AD [5; 59], but other risk factors must be involved as well, since identical twins are known to both develop AD in only 83% of cases [25].

AD can be divided into three broad categories based on the type of genetic contribution known to exist for each category [7]. The first category is for individuals with trysomy 21, or Down syndrome, a condition in which neuropathologic signs of Alzheimer's are almost always present after age 40. The second category includes individuals with familial AD, both early-onset (before age 65) and late-onset (at 65 years of age or older) types. People with

familial AD appear in affected families at a higher rate than do individuals with AD in the general population, the rate being determined by the specific genes they carry. All other individuals with AD belong to the third category of nonfamilial or sporadic AD.

Down syndrome. Persons with Down syndrome, who constitute less than 1% of all cases of AD, have three chromosome 21s. The gene that produces amyloid precursor protein (APP) is located on chromosome 21, and the lifelong over-expression of this gene probably leads to excessive production of APP in these individuals [7]. The role of APP molecules in the production of amyloid plaques is discussed in the chapter "Definition" under "Amyloid plaques" on page 7.

Familial AD. Familial AD comprises about 25% of all cases of AD and is ascertained when two or more persons in the last three generations of a family have AD [7]. Most of these cases are late-onset familial AD, occurring at or after age 65, and only a small proportion (less than 2% of all cases of AD) are early-onset familial AD, occurring before age 65. Early-onset familial AD is caused by mutations in one of at least three genes: APP, presenilin 1, and presenilin 2. The child of a parent with one of these abnormal genes has a 50% probability of inheriting the gene, and an individual with only one mutated copy of one of these genes will develop AD if he or she lives long enough. This type of inheritance is called autosomal dominant. In addition, these genes show virtually full penetrance, which means that every person who receives one copy of a defective gene will manifest AD at an age typical for that gene [33:181–182]. People who receive a mutated APP gene develop AD at an average age of 50 years; a mutated presenilin 1 gene causes onset of AD at an average age of 44 years; and a

mutated presenilin 2 gene—which occurs in only six families worldwide—is associated with a wide range of ages of onset before the age of 65 years [2]. A clear connection exists between these familial early-onset genes and the biology of AD, since the APP gene determines the exact construction of APP and the presenilin genes create proteins that are part of the enzyme γ-secretase and that influence where γ-secretase cuts APP [69]. Other genes will likely be identified as causing early-onset familial AD, however, because autosomal dominant patterns of inheritance of AD have been observed in families with no known mutations in APP, presenilin 1, or presenilin 2 [7].

The other familial form of AD is late-onset familial AD, which is not inherited in a clear-cut autosomal dominate manner. Researchers believe late-onset familial AD involves multiple susceptibility genes that, along with environmental influences, only predispose people to developing AD [7]. Only one of these genes, the apolipoprotein E (APOE) gene, has been discovered and definitely linked to late-onset familial AD. Apolipoprotein E transports cholesterol and certain phospholipids into cells, has antioxidant and growth-promoting properties on cells, and interacts with Aβ to reduce its toxicity [56:1224]. The APOE gene occurs in three different forms, or alleles, the ε2, ε3, and ε4 APOE alleles, which appear in 10%, 75%, and 15% of the general population, respectively. Because an individual receives one APOE gene from each parent, its alleles occur in one of six different combinations in each individual. The commonest combination, ε3/ε3, occurs in about 61% of the U.S. population [59:643].

The specific combination of APOE alleles one inherits determines one's likelihood of developing AD, as well as the typical age of onset of the disease. Further, APOE genotype is

believed to account for as much as 95% of one's risk of developing AD [59]. Table III-1 shows the percent of individuals over 60 years of age with AD with each of the six possible APOE genotypes, as determined by a study of over 5,000 people in the U.S. with AD [5:159]. Relative to the risk associated with the common ε3/ε3 genotype, significantly higher risk was associated with the ε2/ε4, ε3/ε4, and ε4/ε4 genotypes, and significantly lower risk is associated with the ε2/ε2 and ε2/ε3 genotypes [21]. Table III-1 also shows the percent of the entire U.S. population with each genotype [59:643], so that both the prevalence of each genotype and its potency in causing AD are presented. For example, although only 2% of the population in this study had the ε4/ε4 genotype, 72% of people over the age of 60 with the ε4/ε4 genotype had AD [5:159]. Studies of AD and APOE genotype also consistently show that possession of ε4 alleles tends to lower the typical age of onset of AD by roughly 2–8 years, depending on whether the genotype is ε3/ε4 or ε4/ε4, compared to the average age of onset associated with the ε3/ε3 genotype [59:645].

Table III-2, based on data from 18 different studies from around the world [26:6], shows the percent of people with AD with any genotype in each of seven age groups and is useful for putting the rates of AD for specific genotypes into perspective: regardless of genotype, the risk of developing AD increases dramatically with age. In contrast, the cumulate lifetime risk (again without regard for genotype) of developing AD, which is corrected for life expectancy and other factors, is 10.4% [7]. The risks of developing AD associated with specific genotypes vary significantly among ethnic and geographic populations, but in all groups studied, the prevalence of AD among women at all ages is slightly higher than the prevalence among men

Table III-1:
Frequency of APOE Genotypes in US Population and Rate of AD for Each Genotype

Genotype	Percent of US Population with Each Genotype[a]	Percent of White Americans over 60 with AD[b]
ε2/ε2	0.5	2.2
ε2/ε3	11.0	3.3
ε2/ε4	2.0	8.7
ε3/ε3	61.0	5.2
ε3/ε4	23.0	17.0
ε4/ε4	2.0	71.8
Total	99.5	8.7[c]

[a][59:643]
[b][5:159]
[c]Weighted average of all frequencies.

[26:4]. Finally, scientists believe an additional four to seven risk-factor genes for late-onset familial AD likely exist in addition to APOE but are yet to be identified [54:41].

The risk of developing AD for a first-degree biological relative (parents, siblings, or children) of an individual with AD (proband) has been estimated relative to the APOE genotype of the proband [29]. In this study, the cumulative risk of developing AD by age 85 years was estimated for each genotype and used as the measure of risk. Note that cumulative risk estimates for an age *range* are larger than absolute risk estimates for the *ending age*. In this study, the combined cumulative risk for the ε2/ε2, ε2/ε3, and ε3/ε3 genotypes was used as a baseline, and risks were estimated separately for African-American relatives and white American relatives for a combined ε2/ε4–ε3/ε4 group and a ε4/ε4 group. Partial results of the study are summarized in Table III-3. The risk ratios in Table III-3 are the ratios of the cumulative risk for

Table III-2:
Estimates of the Rate of AD by Age Group Worldwide[a]

Age in Years	Percent with AD
65–69	1.1
70–74	2.2
75–79	4.6
80–84	9.2
85–89	17.8
90–94	31.5
95+	52.5
Total	5.7

[a][26:6].

groups ε2/ε4–ε3/ε4 and ε4/ε4ε to the cumulative risk for the ε2/ε2–ε2/ε3–ε3/ε3 baseline group. The risk ratios for the comparison of race alone are the ratios of the cumulative risk for each race to the cumulative risk for white Americans. Among white Americans, the cumulative risk of developing AD for first-degree biological relatives of probands in the ε2/ε4–ε3/ε4 group and in the ε4/ε4 group was 50% greater than the risk associated with the baseline ε2/ε2–ε2/ε3–ε3/ε3 group. Among African Americans, the cumulative risk of developing AD was 30% greater for probands in the ε2/ε4–ε3/ε4 group and 80% greater for probands with the ε4/ε4 group relative to the ε2/ε2–ε2/ε3–ε3/ε3 group. Perhaps the most useful finding of this study is that African-American first-degree relatives of probands of any genotype were 60% more likely than white American relatives of probands of any genotype to develop AD by age 85, the cumulative risk for African-American relatives being 44% and for white American relatives 27%.

Table III-3:
Estimated Cumulative Risk of AD at 85 Years Among First-Degree Biological Relatives of Probands with AD[a]

APOE Genotype of Proband	Cumulative Risk (%)	Risk Ratio
Comparison of Genotypes among White American Relatives		
ε2/ε4 or ε3/ε4	33.6	1.5
ε4/ε4	32.2	1.5
ε2/ε2 or ε2/ε3 or ε3/ε3	22.0	1.0
Comparison of Genotypes among African-American Relatives		
ε2/ε4 or ε3/ε4	47.7	1.3
ε4/ε4	64.6	1.8
ε2/ε2 or ε2/ε3 or ε3/ε3	36.6	1.0
Comparison of African-American Relatives to White American Relatives of All Genotypes		
African Americans	43.7	1.6
White Americans	26.9	1.0

[a][29:332].

Nonfamilial AD. Nonfamilial, or sporadic, AD comprises about 75% of all cases of AD. Nonfamilial AD is ascertained when an individual is diagnosed with AD but has a negative family history for AD in the last 3 generations [7]. It can occur any time in adulthood. First-degree biological relatives of individuals with nonfamilial AD have a cumulative lifetime risk of developing AD of roughly 20% [7]. The range in various studies of this risk is 15–30% [7]. The risk is conservatively estimated to be about twice the 10.4% cumulative lifetime risk of developing AD for individuals without a family history of AD [33:182].

Other Risk Factors

One's genetic complement and one's age are powerful factors determining one's risk of developing AD, but other risk factors also influence one's overall risk. All risk factors can be classified as either nonmodifiable or modifiable depending on whether they can be altered by human intervention. Among the nonmodifiable risk factors for developing AD are genetic status and family history of AD, discussed above, but age, sex, and ethnicity are also nonmodifiable risk factors. Modifiable risk factors include lifestyle, medical, and environmental conditions.

Nonmodifiable risk factors. These factors, which include genetic status and family history, cannot be altered. They include age, sex, and ethnicity:

- **Age.** In the US, the prevalence of AD for persons 65–70 years old is about 1.5%, and this rate approximately doubles with each 5-year increase in age until age 90–95, when the prevalence is about 44.5% [16:132]. Various theories have been developed to explain why aging influences the probability of developing AD. For example, metabolic decline (such as reduced cerebral circulation) that comes with aging promotes the creation of free radicals, highly reactive molecules that can degrade neuron proteins and membranes and that may cause AD neuropathology. Damage done by free radicals, known as oxidative stress, has a wide-ranging cascade of effects on cell physiology [52:70; 56:1225]. Another theory connecting aging and AD relates the production of abnormal APP and other abnormal proteins to mutations of messenger RNA that increase with age [52:70].

- **Gender.** Studies comparing the prevalence of AD among men and women have usually found a slightly higher prevalence among women [26:4]. However, prevalence, the number of people in a specific age group with a disease, is influenced by the survival rate of people with the disease: the longer patients survive with a disease, the more likely they are to be counted in successive age groups. If women survive longer with AD than men, for example, the prevalence of women with AD in later age groups will be higher than the prevalence of men with AD even if the rate at which men and women contract AD is the same. Incidence, on the other hand, is the number of people who contract a disease in a specific age group and is not influenced by survival rate. When incidence is used as a measure of risk, men appear more at risk for developing AD before age 80 and women more at risk after age 80. At age 75, women can be diagnosed with AD at about 80% of the rate at which men can be diagnosed, and at age 85, women can be diagnosed with AD at about 170% of the rate at which men can be diagnosed [42].

- **Ethnicity.** The prevalence and incidence of AD also differs among ethnic groups. In the US, the cumulative risk for developing AD by age 90 has been estimated to be four times higher for African Americans than for white Americans [29]. Hispanic Americans also appear to have higher rates of AD than white Americans, while native Americans appear to have lower rates [49:96]. In general, these findings have been confirmed by other epidemiological studies [49:96]. Although rates of AD also appear to vary from country to country (for example, Japan appears to have lower rates of AD

than does the US), geographic differences are difficult to ascertain with certainty because inconsistent research methods are used in different studies [32:S3].

Modifiable risk factors. A wide range of potentially modifiable risk factors have been associated with AD. These factors include dietary habits, cardiovascular health, life-style choices, educational attainment, psychological stress, hormone levels, head injury, metal toxicity, medical illnesses, environmental toxins, and the use of nonsteroidal anti-inflammatory drugs. The quality and reliability of research into modifiable AD risk factors is variable, however, and in many cases, scientific findings are inconsistent or insufficient for reaching firm conclusions linking AD with a risk factor [32:S9].

- **Diet.** Many research findings on the relationship between diet and AD are inconclusive or unreplicated [16:134–135]. For example, two large-scale studies of the effects on AD risk of consuming large amounts of omega-3 fatty acids (found mainly in cold-water fish such as salmon or tuna) produced contradictory results, one study finding an association between increased consumption of fish and reduced risk for AD and the other study finding no association. In another study, diets higher in polyunsaturated and vegetable fats were associated with reduced risk of AD, but additional research is needed before these diets can be recommended [54:47]. Similarly, studies of the association between taking antioxidant vitamins, such as vitamins E and C, and the risk of AD have produced conflicting results, suggesting that the effect of taking these vitamins is “relatively weak, if it exists at all” [16:135]. Finally, low levels of folic acid and B vitamins have been associated with elevated levels of homocysteine, an amino

acid that is a risk factor for heart disease, and all three are associated with an increased risk of AD [39:57]. However, research using B vitamins to prevent or delay the onset of AD has also produced "mixed results and conflicting recommendations" [16:135]. Although the relationship between dietary factors and the risk of AD may be weak or unproven, research on diet and AD continues, and a healthy diet and the use of vitamin supplements are wise and practical precautions [16:135].

- **Cardiovascular health.** In general, research supports the notion that factors associated with a higher risk of developing cardiovascular disease are associated with an increased risk of developing AD [54:49–52]. Assessing this association is complicated since cerebrovascular disease, such as small infarctions (blockages in arteries) in the brain, also causes a dementia, called vascular dementia, that is often present with AD and worsens the presentation of AD dementia [54:49–52]. In any case, research shows a strong relationship between hypertension, high triglyceride levels, low HDL levels, obesity, nonfatal stroke, smoking, and insulin resistance and an increased risk of dementia [16:135–136; 54:51]. Although some studies show a "mild statistical increase" in AD risk associated with higher cholesterol levels, others do not [16:136].

- **Lifestyle.** The risk of developing AD may also be influenced by such lifestyle choices as level of alcohol consumption, amount of physical exercise, and amount of intellectual and social activity. A low to moderate intake of wine (up to three glasses per day) but not of beer or liquor has been associated with a 50% lower risk of developing AD [43:448], although the association appears to be weaker for people with an APOE ε4

allele [16:137]. Further, epidemiological studies in general have found lowered risks of dementia, stroke, and heart disease associated with a low to moderate intake of wine and an increased risk of dementia associated with higher doses [16:137]. Physical exercise, as a rule, benefits both physical and mental well-being, and some studies have found evidence that low-intensity exercise, such as walking 2 or more miles a day, lowers the risk of developing AD for people at midlife and for the elderly. Exercise likely has many benefits, such as relieving stress, for both AD patients and caregivers [16:137–138]. Finally, intellectual stimulation, social interaction [16:138], and participation in leisure activities [54:48] have also been associated with a decreased likelihood of developing AD, although it is not clear whether these activities are actually protective against AD.

- **Education.** Many, but not all, studies show an increased risk of AD associated with lower levels of education [32:S10–S11], and the connection between the two is well established [16:138–140]. Authorities believe, however, that level of education itself is likely not directly linked to risk for AD but is instead correlated with some other risk factor, such as intelligence. People with higher intelligence may have a greater capacity (cognitive reserve), either biologically or intellectually, to compensate for the physiological losses caused by AD. In addition, better-educated people may perform better on the cognitive tests used to diagnose AD, a problem known as ascertainment bias [16:138–140]. Finally, lower educational attainment is correlated with lower family income and, in theory, with exposure to more environmental risks during childhood [32:10–11].

- **Stress.** Only one study has investigated whether psychological stress is related to risk for developing AD, and although results indicated that people more prone to experience stress were more likely to develop AD, more research is needed to confirm the finding [16:140]. Stronger evidence supports the finding of an association between anxiety and depression and AD risk, although anxiety and depression can also be early symptoms of AD [16:81–89; 140].

- **Hormones.** Researchers have also investigated the relationship between hormone levels and AD risk. One major study of the use of estrogen supplements with older women years after menopause found that the risk of developing AD for women taking supplements actually doubled. Additional research into the effects of estrogen supplementation (for example, with premenopausal treatment), which in theory should improve cognitive functioning, is planned [54:56]. Another major study yielded strong evidence that reduced levels of free testosterone in men is associated with a higher risk of developing AD. Although a few small studies have shown some positive results using testosterone to treat males with AD, larger studies are needed to confirm this finding [16:140; 54:56].

- **Head injury.** Many studies show an association between a history of head trauma sufficient to cause loss of consciousness and later development of AD, finding an approximately 50% greater risk of developing AD after injury earlier in life. This association only exists for males, however [16:140]. Possession of a APOE ε4 allele along with head trauma significantly adds to the increased risk [52:70].

- **Metals.** Although some investigators once believed the amount of aluminum in water supplies was linked to the risk of developing AD, the association has been disproved by more rigorous studies [52:70–71]. This issue has been investigated in many ways, all of which have failed to find a relationship between aluminum exposure and AD [52:70–71], and most researchers believe there is none [16:141]. Also, *in vitro* experiments have suggested that elevated levels of zinc could be associated with increased risk for AD [32:12]. However, although research on zinc continues, studies have yet to detect an association between zinc and AD pathology within the human brain [22]. Attempts to relate exposure to mercury or iron to AD risk have also found no significant association between these metals and AD [39:56].

- **Illness.** Researchers have tried to detect links between a variety of medical illnesses and increased risk of AD. Hypothyroidism in some cases may cause a type of reversible dementia that can resemble AD, but it is otherwise unassociated with AD [16:59]. On the other hand, a few recent studies [18; 35] have shown an association between subclinical hyperthyroidism and an increased AD risk. Studies have also found an increased risk of developing AD in people with insulin-dependent diabetes [32:S11–S12].

- **Environmental toxins.** Although sporadic reports have claimed to detect an association between AD risk and industrial pollutants, pesticides, and electromagnetic fields, these investigations have studied relatively small numbers of people exposed to possi-

ble toxic agents, and their results require corroboration from better-designed studies [32:S12]. To date, no environmental toxin is known to be associated with AD risk [7].

- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Many investigators have reported an association between rheumatoid arthritis, the use of NSAIDs, such as ibuprofen and naproxen sodium, and lowered risk for AD [32:11]. Further, laboratory research suggests that some NSAIDs alter the location at which γ-secretase cuts APP, shifting the cleavage site in a way that produces shorter Aβ peptides (without reducing the overall amount of plaque accumulation) [52:68; 65]. However, “so far, no clinical trial has shown a beneficial effect of NSAIDs on AD prevention or progression,” although research continues on the use of NSAIDs for AD [54:38]. In addition, a recent analysis of epidemiological studies linking the use of NSAIDs to lowered AD risk suggests that findings of an apparent beneficial affect of NSAIDs may largely be the result of defects in research methodology [10]. Current practice guidelines warn of “insufficient evidence” of the effectiveness of NSAIDs and of the “risk of significant side effects” with their use [19:1158].

IV. DIAGNOSING ALZHEIMER'S DISEASE

Diagnosing AD requires ruling out many other causes of dementia as well as finding a history and symptoms typical of AD. Determining which type of dementia a patient has can be difficult because reliable, definitive tests are not available for most of the major dementias.

Overview of Alzheimer's Disease Diagnosis

Currently, there is no reliable laboratory test for AD, and with the exception of the rare early-onset familial types of AD, genetic testing is also inadequate for reliable diagnosis [13:3] since knowing the results of APOE genotyping for a patient only marginally improves the accuracy of a diagnosis made by clinical means [38:1147–1148]. Therefore, diagnosis of AD is a clinical rather than a laboratory process: a patient's medical history, medical condition, and mental functioning are examined in detail; and the signs, symptoms, and history of the patient's illness are used to determine whether the patient has a dementia, and if so, the most likely cause of the dementia. Although the results of laboratory tests will definitively rule out certain causes of dementia, there are no laboratory tests (other than autopsy or biopsy studies) that can establish a diagnosis of AD with certainty. Thus, AD is diagnosed clinically when findings about a patient's history and current condition best fit the pattern seen in AD. Most studies show that the clinical diagnosis of AD is 85–90% accurate, as verified by autopsy, when performed by clinicians experienced in diagnosing dementia [13:3; 15:54–55]. In the US, primary-care physicians often make an initial assessment of possible dementia but normally refer patients to a specialist, usually a neurologist or geriatric psychiatrist, for diagnosis [36].

Although there is no standard procedure for diagnosing AD, certain basic investigations are essential for ruling out other illnesses and arriving at a diagnosis [8; 15; 62; 66]. The physician must look for signs of major neurodegenerative disease as well as of systemic and neurologic diseases or injuries that can cause dementia, including infections, head injury, diseases causing reduced cerebral blood flow, metabolic diseases, and the toxic effects of drugs [62:78]. These are the basic parts of a comprehensive dementia examination [8]:

- **History-taking.** The history taken for a dementia patient should include a general medical history; a history of neurologic disease or injury; a history of cognitive and behavioral impairments; a psychiatric history; a history of toxic, nutritional, medication, and drug problems; and a familial history. Whenever possible, a member of the patient's family should assist in answering questions about the patient's history.

- **Physical examination.** The physical examination of a dementia patient consists of a general medical examination and a comprehensive neurologic examination. The neurologic examination, which includes assessment of the patient's current cognitive functioning, is essential for establishing the presence of dementia.

- **Laboratory tests.** Basic laboratory tests are performed with a dementia patient to rule out the presence of diseases that can produce symptoms of dementia but that are not neurodegenerative. In some cases, brain scans may help in reaching a diagnosis when a neurodegenerative disease is suspected but its type cannot be determined.

- **Differential diagnosis.** The physician or neurologist considers the information gathered by the dementia examination along with standard criteria for the diagnosis of dementia and AD. He or she determines whether the patient is demented and whether AD is the likely cause of the dementia or whether some other disease process is responsible.

History-Taking

A history taken for a patient with suspected dementia assesses signs and symptoms of cognitive decline as well as the patient's history of illness or injury that might cause dementia. The history is taken in these areas:

General medical history. The purpose of the general medical history is to assess the patient for serious medical illnesses that cause or exacerbate dementia. These illnesses include [8:59; 16:57–67]:

- Endocrine disorders, such as hypothyroidism
- Metabolic disorders, such as advanced kidney, liver, or lung disease
- Chronic infections, such a syphilis or AIDS
- Chronic heart disease or hypertension
- Other chronic systemic disease, such as diabetes or connective tissue disorders

History of neurologic illness. The patient's history of neurologic disease or injury reveals neurologic conditions other than neurodegenerative diseases that can cause dementia. These nonneurodegenerative conditions include [8:59]:

- Cerebrovascular illness, such a transient ischemic attacks, strokes, or carotid surgery
- Brain tumors
- Head trauma with or without intracranial surgery
- Infections of the central nervous system, such as encephalitis or meningitis
- Epilepsy
- Other conditions requiring neurosurgery

History of cognitive and behavioral impairments. The history of the patient's cognitive and behavioral functioning focuses on specific symptoms of cognitive impairment and the degree to which these limit the patient's day-to-day activities. The following areas are assessed [8:59]:

- Memory impairment
- Impairment in temporal or spatial orientation
- Language impairment
- Impairment in recognizing people or objects
- Impairment in executive functioning (planning, organizing, reasoning), including the ability to travel, handle money, and make decisions
- Changes in behavior or personality

Psychiatric history. A psychiatric history determines whether the patient has a pure psychiatric disease, dementia associated with a psychiatric disease, or psychiatric symptoms caused by a primary dementing illness. The following areas are assessed [8:59–60]:

- History of depression and current depressive symptoms
- History of psychosis, including delusions, hallucinations, or paranoid ideation
- History of personality changes, including aggressive or other inappropriate behaviors

Toxic, nutritional, medication, and drug history. Taking a history of toxic, nutritional, medication, and drug exposure screens further for extraneous factors that may cause cognitive decline. The following areas are assessed [8:60–61]:

- Exposure to toxins, such as glues, pesticides, or fertilizers
- Chronic nutritional deficiencies, such as vitamin B_{12} deficiency
- Chronic alcoholism
- Chronic use of medications, over-the-counter drugs, or herbal medicines

Familial history. Taking a history of major illnesses in the patient's family may suggest illnesses to which the patient is particularly susceptible and that may cause or exacerbate dementia. These illnesses include [8:61; 16:64]:

- Cardiovascular and other systemic general medical conditions
- Dementias, including AD

- Other neurologic diseases, such as Parkinson's disease or Down's syndrome
- Psychiatric illnesses, particularly depression

Physical Examination

After the physician takes a thorough medical history for the dementia patient, he or she performs a physical examination, the second major part of a comprehensive dementia examination. The physical examination consists of a general medical examination and a comprehensive neurologic examination.

General medical examination. The general medical examination for a dementia patient consists of a basic medical examination, examination for medical conditions noted in the patient's history, and examination for risk factors associated with dementia. The examination includes [8:61]:

- Evaluation of overall physical status and vital signs
- Screening for arteriosclerosis and other cardiovascular risk factors, such as heart disease, high blood pressure, or aneurysms and other vascular disease
- Screening for signs of other systemic illness, such as enlarged lymph nodes or symptoms of endocrine disorders or organ failure

Comprehensive neurologic examination. The comprehensive neurologic examination assesses the patient for signs of neurologic illness and systematically evaluates the patient's cognitive functioning. The patient is examined for [8:61; 66:705–706]:

- Signs of abnormal intracranial pressure
- Focal (specific, isolated) neurologic deficits, such as a gait disturbance, motor or sensory deficit, or visual field defect
- Abnormal muscle tone, movements, or reflexes
- Deficits in cognitive functions, including:
    - Attention
    - Orientation (to time, place, and person)
    - Memory (immediate, short-term, and long-term)
    - Language and related skills (including calculation and writing)
    - Learned movement (such as pantomiming the use of a common object)
    - Sensory recognition (such as recognizing an object by touch alone)
    - Visuospatial and visuoperceptual abilities (used, for example, in drawing a simple design)
    - Executive functioning (planning, reasoning, judgement)
    - Appropriate interpersonal behavior

The process of assessing the intellectual functioning of a dementia patient usually includes administering a cognitive screening test. These tests measure a range of intellectual abilities and yield a numeric score (and sometimes subscores) indicating the level of the patient's cognitive functioning. A screening test widely used in practice and research is the Mini Mental Status Examination (MMSE), shown in Appendix A on page 79. The MMSE takes about 10 minutes to administer and is used to screen for signs of dementia and to make repeated assessments of a patient over time. The MMSE has limitations: it does not assess some kinds of

intellectual abilities; its scores can be influenced by the patient's level of educational attainment; and it is limited in its capacity to distinguish between different causes of dementia [66:707]. The MMSE score should be interpreted, therefore, in the context of the other results of the dementia examination. The MMSE samples a patient's performance in areas of orientation; attention; memory; language and math; planning; and visuomotor skill. Scores on the test can range between 0 and 30. In general, scores of 27 or higher are considered normal; scores between 23 and 26 are considered borderline; and scores of 22 or below are considered abnormal. For AD patients, scores from 20–26 suggest mild AD; scores from 10–19 suggest moderate AD; and scores less than 10 suggest severe AD [16:34]. Figure IV-1 shows how the

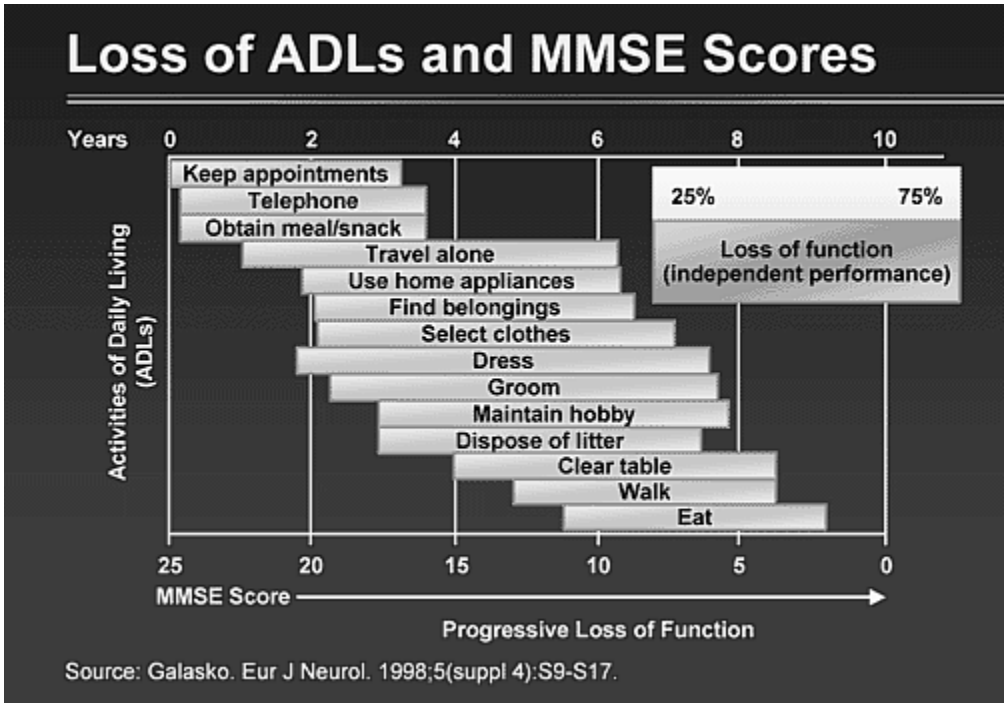


Figure IV-1: The number of AD patients who lose the ability to perform activities of daily living increases with declining MMSE scores [24].

percentage of AD patients who lose the ability to perform various activities of daily living

(ADLs) is related to MMSE score and to number of years since diagnosis. For example, the ability to find one's belongings is lost by 25% of patients with an MMSE score of 20 and by 75% of patients with an MMSE score of 9.

The MMSE is a very cost-effective test, since it provides limited but very useful information quickly. A more detailed assessment of cognitive abilities in a dementia patient can be made through the use of neuropsychological testing. However, outside the research setting such testing is not recommended for routine assessment if a diagnosis can be reached using the other findings of a dementia examination. Neuropsychological tests take considerably longer to administer than screening tests; in-depth testing can take two days to complete. Some newer tests, however, are designed specifically to assess dementia and aid in differentiating between neurodegenerative diseases. Neuropsychological testing is considered useful when the type of dementia cannot be determined, when psychiatric problems are present along with dementia, or when legal issues make an evaluation of mental competence necessary [15:39–40; 16:40–41].

Finally, the mental functioning and medical history of a dementia patient can be reported to the clinician by an informant, a family member of other caregiver who knows the patient. Screening questionnaires for informants, which also yield numeric scores estimating the cognitive or functional abilities of patients, are available for this purpose. One such test is the Blessed Dementia Rating Scale [58:1140].

Laboratory Tests

The physical examination of dementia patients usually includes using common and specialized laboratory tests to help rule out systemic illnesses that can cause cognitive impairment. For example, physicians may order a brain scan for a dementia patient if a neurodegenerative disease is suspected but the type of disease is unclear or if another neurologic illness, such as cerebrovascular disease, is believed to be present along with the primary dementing disease. Other laboratory tests, including genetic testing, have a role in dementia evaluation in special circumstances.

Traditional laboratory tests. In ordering laboratory tests for a dementia patient, the physician is guided by the patient's history and physical examination. A few laboratory tests, however, are recommended for routine use in a dementia evaluation. The American Academy of Neurology currently recommends that only two laboratory tests, which studies show have good diagnostic value, be routinely used with dementia patients [38:1149]. However, experts often advise using additional tests. These recommended and optional tests and their rationales are summarized in the Table IV-1.

Lumbar puncture. Lumbar puncture is not routinely performed with dementia patients. Lumbar puncture draws a sample of cerebrospinal fluid (CSF) for laboratory analysis and is useful in detecting rare types of dementia caused by infectious agents, such as certain fungi, tuberculosis, and syphilis [16:44–45]. In addition, levels of CSF amyloid, the Aβ42 peptide specifically, and tau protein can also be measured by lumbar puncture. When Aβ42 is lower than normal and tau is higher than normal, AD is indicated. This test, which accurately detects

Table IV-1:
Laboratory Tests used with Dementia Patients

Test	Rationale
Tests Recommended by the American Academy of Neurology[a]	
Vitamin B_{12} level	Dementia attributable to Vitamin B_{12} deficiency is found in a very small number of dementia patients.
Thyroid function analysis	Dementia attributable to hypothyroidism is found in a very small number of dementia patients.
Optional Tests Recommended by Experts[b]	
Complete blood count	Infections and immunodeficiency syndromes are associated with impaired cognitive functioning.
Comprehensive chemistry panel	Liver and kidney failure and diabetes are associated with impaired cognitive functioning.
Folate level	Folic acid deficiency is associated with impaired cognitive functioning.
Erythrocyte sedimentation rate	Autoimmune diseases, such as systemic lupus, are associated with impaired cognitive functioning.
Liver function tests	Liver dysfunction is associated with impaired cognitive functioning.
Venereal Disease Research Laboratory test for syphilis	Advanced syphilis causes dementia.

[a][38:1149]
[b][16:42–43; 40]

AD about 85% of the time, is commercially available but is not recommended for routine use, since clinical diagnosis of AD by an experienced neurologist is correct about 85–90% of the time, and because lumbar puncture is expensive and may have unpleasant side effects [16:44–45; 38:1147–1148].

Several other tests of levels of substances in CSF associated with AD exist. However, none of these tests for CSF biomarkers of AD increase the diagnostic accuracy of competent clinical diagnosis, and none are recommended for routine use with patients with suspected AD [38:1148]. A test of CSF is recommended, however, if the neurodegenerative illness Creutzfeldt–Jacob disease is suspected, since a reliable CSF test is available for that disease [38:1148].

Brain scans and electroencephalogram. A computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain is appropriate in routine initial evaluations of patients with dementia [38:1148]. An electroencephalogram (EEG) is appropriate if the dementia patient also suffers from seizures [16:43–44].

Noncontrast CT scans and MRI, which provide structural imaging of the brain, are useful in dementia assessment for ruling out certain neurologic illnesses, such as brain tumors, strokes, blood clots, or hydrocephalus. CT scans and MRI with contrast, in which the patient is injected with an agent to improve visualization of brain structures, may also be appropriate if used to rule out certain types of brain lesions, such as tumors. On the other hand, Quantitative CT scans and MRI, in which the volume of brain structures is measured, have not been shown to increase diagnostic accuracy over nonquantitative scans. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) both measure metabolic activity in the brain. However, neither of these tests is recommended for use in the diagnostic evaluation of dementia, since studies have not demonstrated that PET or SPECT results increase the accuracy of diagnosis made by established clinical criteria [38:1147–1148].

While CT scans and MRI can provide images of brain structure, the EEG provides a primitive assessment of brain functioning by revealing the frequency of waveforms generated by electrical activity in the brain. However, although a reduction in these frequencies is seen in patients with AD, a reduction is caused by many other disease states as well. In addition, changes in EEG frequency with AD occur only after the disease is clinically obvious. Although an EEG is therefore inappropriate for use in the routine diagnosis of AD, some patients with AD also experience seizures, and with these patients an EEG is needed to evaluate seizure activity [16:43–44].

Genetic testing. APOE genotyping is considered inappropriate for use with asymptomatic individuals (those for whom there is no evidence of AD), since having one or even two ε4 alleles, while increasing one's lifetime risk of getting AD, does not increase it greatly enough to be a useful basis for genetic counseling. In addition, a significant proportion of people with AD have no ε4 alleles. Routine use of APOE genotyping with patients with suspected AD is also considered inappropriate in most cases, since studies show that considering APOE test results when an AD evaluation is inconclusive only marginally improves accuracy of diagnosis [16:132–134; 38:1147–1149].

The rare, early-onset familial forms of AD are inherited in an autosomal dominant manner: individuals who possess one of the genes causing early-onset familial AD will develop AD if they live long enough. Although tests for most of these genes are commercially available, expertise in genetic counseling for asymptomatic individuals at risk for early-onset familial AD is available only in specialized dementia research centers [38:1147]. Early studies show

that relatively few such individuals choose genetic testing, that those who choose to have the tests usually cope well with positive results when provided competent counseling, but that some who receive positive test results experience significant depression [7].

Differential Diagnosis

Following a history-taking, a physical examination, and laboratory tests, the physician conducting a comprehensive dementia examination must review his or her findings by making a differential diagnosis. Differential diagnosis is a decision-making process in which (1) all diseases that may cause a patient's illness are first included for consideration (ruled in), and (2) diseases are excluded (ruled out) one-by-one by determining whether the characteristic signs of each disease are seen in the patient. In assessing a dementia patient, differential diagnosis occurs at three points. The clinician must decide (1) whether dementia or some other condition, principally depression or delirium, is causing the patient's cognitive impairment, (2) whether a neurodegenerative condition or a nonneurodegenerative condition (e.g., hypothyroidism or tumor) is causing the patient's dementia, and (3) whether the patient's neurodegenerative illness is caused by AD or some other neurodegenerative disease (e.g., frontotemporal dementia). By the time a thorough dementia evaluation is completed, the physician should have enough information about the patient's history and condition to decide whether the patient suffers from dementia and, if so, to rule out as its cause many illnesses whose features are plainly inconsistent with evaluation results. Nonneurodegenerative illnesses are ruled in or out early, because symptoms and test results for these illnesses are relatively unambiguous. Many of these illnesses can be treated successfully.

Criteria for diagnosing dementia and AD. When determining whether a patient has dementia or AD, clinicians refer to specific criteria for these diseases established by medical and research associations. The criteria make differential diagnosis more uniform and reliable. Dementia, for example, is broadly defined by T.J.Grabowski and A.R. Damasio as an "acquired and persistent impairment of intellectual faculties, affecting several cognitive domains, that is sufficiently severe to impair competence in daily living, occupation, or social interaction" [28:2]. The American Psychiatric Association (APA) publishes specific criteria for diagnosing dementia, shown in Table IV-2, that are widely used in practice and research [4:133–143]. The APA criteria for dementia require that a patient have both memory impair-

Table IV-2
American Psychiatric Association Criteria for Dementia[a]

A. The development of multiple cognitive deficits manifested by both:
    1. memory impairment (impaired ability to learn new information or recall previously learned information)
    2. one (or more) of the following cognitive disturbances:
        a. aphasia (language disturbance)
        b. apraxia (impaired ability to carry out motor activities despite intact motor function)
        c. agnosia (failure to recognize or identify objects despite intact sensory function)
        d. disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The deficits do not occur exclusively during the course of a delirium.

[a][4:133–143].

ment and one other form of cognitive impairment. This requirement is somewhat controversial, since many clinicians and researchers wish to diagnose patients who initially display only progressive memory impairment as having dementia (usually AD), and wish to classify as having dementia patients with multiple cognitive deficits but without memory impairment, a pattern present in many common neurodegenerative illnesses [16:6; 37:1292]. The APA system classifies a condition characterized by deficits in memory but in no other cognitive domain and having no known etiology as Amnestic Disorder Not Otherwise Specified. [4:163].

After a clinician diagnoses dementia, he or she may refer to either of two widely used sets of criteria to establish a diagnosis of AD, one developed by the APA [4:142–143] and one by the National Institute of Neurologic and Communicable Diseases–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) [15:44–45]. The NINCDS–ADRDA criteria are most often used to diagnose AD, particularly in research settings, because they allow the clinician to indicate whether the patient's condition is probable, possible, or definite AD. In addition, the NINCDS–ADRDA criteria allow a patient to be diagnosed with possible AD who exhibits memory impairment with no other cognitive deficit. Both sets of criteria incorporate a requirement that the patient have dementia. The APA and NINCDS–ADRDA criteria for AD are shown in Tables IV-3 and IV-4, respectively.

Differential diagnosis—dementia, delirium, or depression? Dementia produces symptoms of cognitive decline but so do delirium and depression, which must, therefore, be ruled out to arrive at a diagnosis of dementia.

Table IV-3:
American Psychiatric Association Criteria for Dementia of the Alzheimer's Type[a]

A. The development of multiple cognitive deficits manifested by both:
    1. memory impairment (impaired ability to learn new information or recall previously learned information)
    2. one (or more) of the following cognitive disturbances:
        a. aphasia (language disturbance)
        b. apraxia (impaired ability to carry out motor activities despite intact motor function)
        c. agnosia (failure to recognize or identify objects despite intact sensory function)
        d. disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
    1. other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
    2. systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
    3. substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another psychiatric disorder (e.g., Major Depressive Disorder, Schizophrenia)

[a][4:142–143].

Delirium is an acute disturbance in consciousness and cognition that develops over a short period of time, usually hours or days, tends to fluctuate during the course of the day, and is usually the direct result of a general medical condition (e.g., the delirium associated with

fever). With delirium, a patient's ability to focus or sustain attention is so severely impaired that an examiner may be unable to engage the patient in conversation. A patient with delirium is usually clearly disoriented and may experience hallucinations, delusions, and memory impairment. Delirium is distinguishable from early dementia by all of these features except memory impairment. Disorientation and clouded consciousness, in particular, appear relatively late in the course of dementia but early in delirium, as do hallucinations and delusions [4:124–127; 46].

Depression may also cause decline in cognitive functioning, including memory. If depression is suspected on the basis of the patient's history or examination, the clinician assesses the patient for depression, making a referral to a mental health professional if necessary. Disturbance of mood is the hallmark of depression. In addition, depressed patients usually exhibit impaired motivation in cognitive testing, tend to overstate the degree of intellectual decline they experience, and have intact language and motor skills. Disturbances of mood appear relatively late in the course of dementia. In addition, dementia patients typically are motivated to perform well on cognitive tests, tend to minimize or rationalize symptoms of cognitive decline, and in more advanced cases, have deficits in language and other abilities. [46; 62:79; 68].

Differential diagnosis—which type of dementia? Once a clinician has ruled out depression and delirium and has diagnosed dementia, he or she must rule out many causes of dementia to arrive at a diagnosis of AD. These causes can be classified into three categories [8:63]:

Table IV-4:
NINCDS–ADRDA Criteria for Diagnosis of AD[a]

Criteria for the Diagnosis of Probable AD

Basic Criteria—all must be present

- dementia established by clinical examination and documented by the Mini Mental State Test, Blessed Dementia Scale, or some similar examination and confirmed by neuropsychological tests
- deficits in two or more areas of cognition
- progressive worsening of memory and other cognitive functions
- no disturbance of consciousness
- onset between the ages of 40 and 90, most often after the age of 65
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

Diagnosis of Probable AD is Supported by—any may be present

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
- impaired activities of daily living and altered patterns of behavior
- family history of similar disorders, particularly if confirmed neuropathologically
- laboratory results of normal lumbar puncture as evaluated by standard techniques; normal pattern of nonspecific changes in the electroencephalogram, such as increased slow-wave activity; and evidence of cerebral atrophy on computerized tomography (CT), with progression documented by serial observation

Clinical Features Consistent with the Diagnosis of Probable AD—any may be present

- plateaus in the course of progression of the illness
- associated symptoms of depression; insomnia; incontinence; delusions; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; and weight loss
- other neurological abnormalities in some patients, especially with more advanced disease, and including motor signs such as increased muscle tone, myoclonus, or gait disorder
- seizures in advanced disease
- CT normal for age

[a][15:44–45]

(continued)

Table IV-4 (Continued):
NINCDS–ADRDA Criteria for Diagnosis of AD[a]

Features that Make the Diagnosis of Probable AD Uncertain or Unlikely—any may be present

- sudden, apoplectic onset
- focal neurological findings, such as weakness on one side of the body, sensory loss, visual field deficit, or incoordination early in the course of the illness
- seizures or gait disturbances early in the course of the illness

Criteria for the diagnosis of possible AD

Basic Criteria—any may be present

- meets the criteria of probable AD except that variations in the onset, presentation, or clinical course may be present
- presence of a second systemic or brain disorder sufficient to produce dementia but which is not considered the cause of the dementia
- presence of a single, gradually progressive, severe cognitive deficit in the absence of any other identifiable cause (used in research studies)

Criteria for the diagnosis of definite AD

Basic Criteria—all must be present

- the criteria for probable AD are met
- biopsy or autopsy finds AD neuropathology

[a][15:44–45]

- Systemic disease, such as vitamin B_{12} deficiency or hypothyroidism
- Nonneurodegenerative neurologic disease, such as normal pressure hydrocephalus, brain tumors, or chronic meningitis
- Neurodegenerative disease, such as AD or frontotemporal dementia.

In nonneurodegenerative neurologic disease, neurons are degraded or lost through contact with an extraneous process, such as a brain tumor. In neurodegenerative disease, the physiology of the neurons is defective and degeneration is progressive.

In determining the cause of a patient's dementia, differential diagnosis begins with ruling out the presence of systemic diseases and nonneurodegenerative neurologic diseases. Most of these illnesses can be discovered or ruled out relatively easily by a thorough dementia examination—by obtaining a history, assessing physical and mental status, and conducting relevant laboratory and other tests. When systemic and neurologic causes are ruled out, primarily neurodegenerative dementias remain, and they present a challenge for differential diagnosis. Definitive tests do not exist for many of these dementias, and the clinician often bases a diagnosis on a review of the patient's symptoms and the order of their appearance.

The main causes of dementia are four neurodegenerative conditions—AD, frontotemporal dementia, dementia with Lewy bodies, and Creutzfeldt–Jakob disease—and two nonneurodegenerative conditions—vascular dementia and normal pressure hydrocephalus [28:4–7; 30]. Vascular dementia and normal pressure hydrocephalus tend to be progressive and to resemble the neurodegenerative dementias in presentation. A list of these major dementias follows with brief descriptions of their biological causes, clinical presentations, and relevant diagnostic tests. The physician must know the characteristic features of these dementias to complete the process of differential diagnosis.

- **AD.** *Biology*—Filaments of tau protein develop within neurons and masses of Aβ protein form around neurons. Neuron dysfunction and brain atrophy result, beginning in specific areas of the temporal lobe and spreading to most of the brain. Life expectancy after diagnosis ranges between 3–20 years. *Presentation*—Most commonly occurs after age 65. Initially, progressive memory impairment alone is present. Within the first 3 years, deficits in language, visuospatial ability, and spatial orientation develop. Major cognitive decline follows, with impairment to reasoning and judgement. Major personality change, gait impairment, sensory and motor deficits, and disabling neurologic disorders appear late in AD. *Tests*—No specific test for AD exists. Diagnosis is based on clinical symptoms and the order in which they develop. Brain scans can help rule out some other forms of dementia.

- **Frontotemporal dementia.** *Biology*—Filaments of tau protein develop within neurons, but Aβ plaques are not seen. Atrophy occurs in the frontal lobes and usually the temporal lobes. Life expectancy after diagnosis is 8–10 years. *Presentation*—Typically develops in the sixth decade of life. Conspicuous behavioral deficits in areas of social judgement and personality appear first and include aggressive or sexual social inappropriateness, disinhibition, disregard for personal space, lack of empathy, apathy and blunted affect. Slovenliness; repetitive, inflexible behavior; and odd food cravings are also typical. Language impairment is usually present and characterized by reduced, stereotyped speech that eventually develops into mutism. Deficits in memory and visuospatial ability, if present, are mild. *Tests*—Diagnosis is based largely on clinical

criteria. However, structural and metabolic imaging usually reveal atrophy and hypometabolism in both the frontal and temporal regions [16:69–70; 30:693–694].

- **Dementia with Lewy bodies.** *Biology*—Spherical masses of the protein α-synuclein (Lewy bodies) form within neurons and are widespread throughout the brain, but very little brain atrophy is seen. Life expectancy after diagnosis averages 3–6 years but can range up to 20 years. *Presentation*—Age of onset ranges between 50–83. Dementia is an early symptom and includes deficits in attention, visuospatial skills, and memory. Deficits in language are uncommon. Dementia is progressive and is characterized by three main features: frequent, prominent visual hallucinations; marked daily fluctuations in cognitive functioning; and Parkinsonian-like slowness of movement and muscle rigidity. Patients may lack paralysis during REM sleep and physically act out while dreaming. *Tests*—History and clinical examination are critical to diagnosis. Brain imaging has not proven useful, since atrophy is mild and pathology widespread [16:68–69; 30:694–695; 64:14].

- **Creutzfeldt–Jakob disease.** *Biology*—An abnormal protein called a prion (from *proteinaceous infectious particle*) reproduces rapidly in the brain, accumulates within neurons, and causes diffusely scattered vacuolar (spongiform) lesions, astrogliosis (fibrous scarring around damaged areas), and neuronal loss. In most patients, death occurs within 12 months of infection. 85% of cases are sporadic (of unknown cause) rather than familial or iatrogenic. *Presentation*—Occurs at an average age of 60 but is very rare, with an incidence of about 1 per million per year worldwide. Dementia

affecting most areas of cognition is apparent within a few weeks of infection and progresses rapidly. Early in its course, a period characterized by myoclonic muscle jerks and frequent startle responses regularly occurs. Various motor, balance, gait, speech, and visual disturbances are common. *Tests*—A distinct abnormality in EEG is always present. Standard MRI and CSF analysis are normal. However, a special CSF test typically shows elevated levels of the 14-3-3 protein, which are found in few other diseases [16:70; 30:695–697].

- **Vascular dementia.** *Biology*—Stroke, small-vessel ischemia (reduction in blood flow), and atherosclerosis cause reduced blood flow to parts of the brain, compromising neurologic functioning or destroying brain tissue. Multiple lesions in sufficient numbers cause dementia. *Presentation*—Typically begins between the ages of 60 and 75. Focal neurologic symptoms, such as weakness or sensory loss on one side; abrupt onset of speech impairments; or abnormal reflexes are common. Symptoms tend to appear abruptly and progression of dementia tends to follow a stepwise course. Personality is usually preserved. Large numbers of small strokes (small-vessel ischemia) lead to a general slowing and inefficiency of thought, impaired memory retrieval, poor problem solving ability, apathy, and balance and gait problems. Since cerebrovascular disease is common in the elderly, vascular dementia frequently accompanies AD and worsens its presentation. *Tests*—CT and MRI reveal multiple lesions caused by large and small strokes. History and examination typically find vascular disease risk factors, such hypertension, atherosclerosis, or history of strokes [16:65–68; 28:6].

- **Normal pressure hydrocephalus.** *Biology*—Impaired reabsorption of cerebrospinal fluid, which is produced and then reabsorbed by the brain, causes marked enlargement of the ventricles (cavities in the brain filled with cerebrospinal fluid). The ventricles in turn press against surrounding cerebrocortex, although shrinkage of the cortex is slight. Cerebrospinal fluid pressure usually tests normal once the brain has compensated for reduced reabsorption. *Presentation*—Often follows head injury, brain surgery, meningitis, and certain types of hemorrhages. A disturbance of balance and gait (slowed steps, wide base, failure to lift feet from the floor), urinary incontinence, and a progressive dementia are regularly present. Dementia is characterized by slowed mental speed, impairment of attention, and diminished executive functioning (organizing, reasoning, planning). *Tests*—Lumbar puncture reveals normal cerebrospinal fluid pressure. Brain imaging shows enlarged ventricles [15:52–53; 16:59–56; 28:6–7].

A diagnosis of AD is reached when the other major dementias are ruled out. However, as J.L. Cummings and Z.S. Khachaturian observe, diagnostic criteria for many of the dementias are "largely subjective and dependent on clinician expertise" [13:8]. Thus, differential diagnosis of the major dementias can be difficult, and accuracy of diagnosis for some dementias can be disappointing, which T.J. Grabowski and A.R. Damasio explain: "Clinical diagnoses of dementia rely on recognizing patterns of neurological and cognitive impairment, rather than on specific biomarkers or other laboratory approaches. Diagnostic problems arise because the neurological findings are usually nonspecific, and the cognitive profiles may overlap. . . . Problems also arise because the processes that cause dementia are not mutually exclusive, and multiple factors may coexist in any given patient" [28:7–8].

V. STAGES AND SYMPTOMS OF ALZHEIMER'S DISEASE

No signs or symptoms neatly divide the development of AD into phases or stages. By convention, however, the progressive course AD has been divided into three stages: mild, moderate and severe. In addition, researchers have developed more complex stage systems that use standardized rating instruments to assess the patient's condition. The conventional stage model and an example of a complex stage system, the Clinical Dementia Rating scale, are described in this chapter. The cognitive and behavioral symptoms of AD tend to vary by stage. These symptoms and the stages at which they occur are also reviewed.

Stage Model

The stage model is the most commonly used method of describing the progression of AD. It is often used in research on AD as well. The model classifies patients as having either mild, moderate, or severe AD. Practical, informal observations determine a given patient's stage. P. Dash and N. Villemarette–Pittman describe the three stages: "Generally speaking, if the person has some obvious cognitive difficulties, but is reasonably communicative and can still accomplish basic self-care and some complex functions, such as using the telephone and household appliances, then she is considered to be in the *mild* phase. Conversely, if the disease has progressed to the point that nursing home placement has occurred or is imminent, she is labeled *severe*. Circumstances in between mild and severe are labeled *moderate*" [16:34]. Because specific MMSE scores are associated with each stage, a patient's MMSE score can help the physician determine a patient's stage. MMSE scores of 27 or higher are considered

normal, while scores of 20–26 are associated with mild AD, scores of 10–19 with moderate AD, and scores under 10 with severe AD [16: 34, 48].

Clinical Dementia Rating Scale

In addition to the commonly used stage model, other more complex staging systems have been devised primarily by researchers. For example, the Clinical Dementia Rating (CDR) scale was developed for use in medication trials and research where accurate, reliable measurement of abilities used in everyday living is needed for assessing severity of dementia. The CDR can be used in clinical settings as well. The CDR rates the patient's overall level of functioning and provides subscores for memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The overall score and subscores can be 0, 0.5, 1, 2, or 3, which indicate impairment as normal for the patient's age, questionable, mild, moderate, or severe, respectively. The test is administered as a structured interview of both the patient and a family member or other person familiar with the patient. Fifty questions about the patient's functioning are asked of the informant; and 27 are asked of the patient, including questions that assess the patient's memory. Studies indicate that the CDR is a valid and reliable instrument, and it conveniently provides ratings—1, 2, and 3—that correspond to the stages of the stage model [51]. Table V-1 summarizes the abilities a patient possesses in each area of life for each of the five CDR scores.

Researchers have developed other scales that describe how well dementia patients function cognitively and behaviorally, but they are used almost exclusively in research. The discussion

Table V-1:
Relationship of Abilities of Everyday Life to CDR Scores[a]

	Healthy CDR 0	*Very Mild Impairment CDR 0.5*	*Mild CDR 1*	*Moderate CDR 2*	*Severe CDR 3*
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss, only fragments remain
Orientation	Fully orientated	Fully orientated except for slight difficulty with time relationships	Moderate difficulty with time relationships; orientated for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Orientated to person only
Judgment & Problem Solving	Solves everyday problems and business affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	*No pretense of independent function outside home;* appears well enough to be taken to functions outside a family home	*No pretense of independent function outside home;* appears too ill to be taken to functions outside a family home
Home & Hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

[a][51].

of cognitive and noncognitive symptoms of AD that follows uses the stage model to indicate when symptoms typically occur in AD.

Cognitive and Noncognitive Symptoms of Alzheimer's Disease

The symptoms of AD are both cognitive and noncognitive. Cognitive symptoms are evidence of impairment to executive functioning, memory and orientation, basic motor function, abstract thinking, language, learned movement, and recognition of people and objects. Non-cognitive symptoms are psychiatric and behavioral in nature and include personality alterations, delusions, hallucinations, agitation, depression, apathy, anxiety, disinhibition, irritability, purposeless behavior, aberrant motor behavior (e.g., wandering), and disorders of sleep, appetite, and sexual behavior.

Cognitive symptoms. These are the primary cognitive symptoms of AD, which worsen as the disease progresses [8:65–68; 60:1136–1138]:

- **Executive functioning.** Patients with mild AD may begin to have noticeable problems functioning in employment and social situations. Patients with moderate AD may be too impaired intellectually to work and may withdraw from demanding social situations. They may need reminding or assistance with toileting and hygiene. They may also develop cognitive abulia, an inability to carry a thought long enough to carry out purposeful action. At the end of this stage, patients cannot live alone without supervision. Patients with severe AD lose all ability to plan, organize, or problem-solve.

- **Memory and orientation.** Patients with mild AD may experience disorientation for direction and distance in unfamiliar locations, misplace objects of value, forget much of what they have just read, and display a declining knowledge of recent personal and world events. Patients with moderate AD may be disoriented for direction and distance in familiar places. They can easily become disoriented to time and place, have difficulty recalling addresses or phone numbers, sometimes forget the names of close family members, and have a diminishing knowledge of their own past. Patients with severe AD lose most memories, orientation to person, and the ability to remember and recognize familiar voices and faces.

- **Basic motor function.** Patients with mild AD typically show no motor impairment, although some patients may display a mild slowing of movement. Patients with moderate AD may develop slowed movements, slowed gait, and sometimes involuntary muscle contractions (mainly of the hands) or compulsive repetition of gestures. Patients with severe AD may have abnormally strong muscle tone and loss of flexibility, diminished facial expression, and sometimes seizures. They may be incontinent. Eventually these patients lose the ability to walk, hold their heads up, or smile.

- **Abstract thinking.** Patients with mild AD have relatively good insight and ability for abstract thought. Patients with moderate AD show diminishing insight and greater reliance on concrete thinking. Patients with severe AD lose the capacity to reason abstractly.

- **Language.** Patients with mild AD develop mild word-finding difficulty. Patients with moderate AD may have speech that, although fluent, has lapses in meaning. These patients may substitute plainly incorrect words for ones they cannot find, echo what a speaker says to them, or repeat words or phrases compulsively. They show diminished verbal comprehension and have increasing difficulty reading and doing simple math. The speech of patients with severe AD may become sporadic and virtually devoid of meaning. Their voice may be reduced to a whisper due to neurologic impairment, and they may eventually become mute.

- **Learned movement.** Patients with mild AD have normal or slightly impaired visuospatial sense, demonstrated, for example, in difficulty drawing simple designs. Patients with moderate AD may have difficulty imitating motions, performing well-learned motions (such as using a common tool), and organizing complex sequences of actions. Patients at this stage become unable to dress themselves. Patients with severe AD may be unable to undress or perform many other simple daily activities. Eventually, these patients lose their ability to make learned, purposeful movements.

- **Recognition of people and objects.** Patients with mild AD demonstrate subtle forms of impaired recognition only detectable by neurologic testing. Patients with moderate AD develop recognition deficits that usually manifest as difficulties with everyday activities. These deficits include difficulty recognizing objects overlapping each other, recognizing parts of one's own body, recognizing objects by touch, and recognizing objects in one half of one's visual field. Patients at this stage may misidentify others,

misidentify themselves reflected in a mirror, or believe people seen on television are present in the home. Patients with severe AD lose the ability to recognize others with whom they are close.

Noncognitive symptoms. Psychiatric and other behavioral symptoms are common in AD. They place considerable economic and psychological stress on caregivers and are the largest single factor in the decision to institutionalize patients with AD [63]. Moreover, some non-cognitive symptoms typically occur before diagnosis, while the appearance of some, such as psychotic symptoms, frequently cause caregivers to seek a dementia assessment [6]. In one study of when various noncognitive symptoms are most common, 100 people who had cared for AD patients treated at a large university hospital were asked when in the course of the ill-ness various behavioral symptoms were most prominent. The results of the study are summa-rized in Figure V-1, which shows when each behavioral disturbance most frequently occurred during a five-year period extending before and after diagnosis [6]. A variety of noncognitive symptoms occur in AD [11; 12; 16:81–89; 47:66; 48; 55:12]:

- **Depression.** Depression is more common among AD patients than among elderly nor-mal adults and is seen more often in moderate and severe AD than in mild AD. Major depressive episodes are infrequent, but minor depressive syndromes are seen in one-third to one-half of patients with AD.

- **Other disturbances of mood.** Irritability, anger, and lability of mood are found in approximately 40% of AD patients and become more frequent as the disease advances.

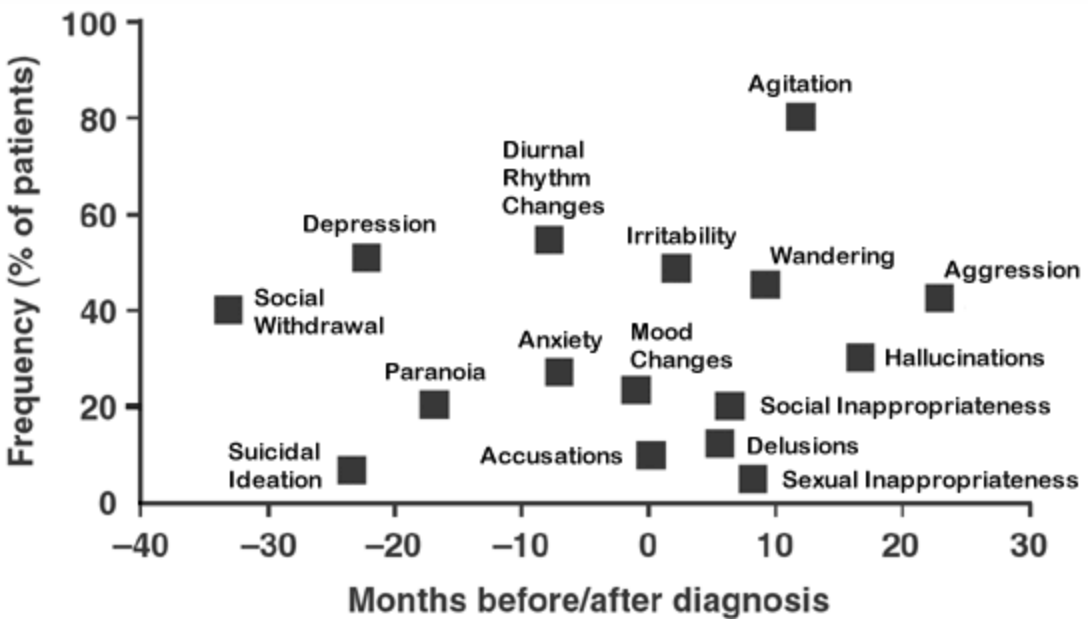


Figure V-1: Peak frequencies of behavioral disturbances in AD patients over a 5-year period [6].

Sometimes catastrophic reactions, major emotional outbursts usually associated with frustration or failure, are seen. These events are short-lived but can involve shouting, cursing, and striking out.

- **Psychosis.** Delusions and hallucinations commonly occur in moderate AD but tend to abate as the disease becomes more severe. Delusions in AD include false beliefs of theft by or infidelity of family members. Some delusional beliefs are based on misi-dentification syndromes. For example, an AD patient may believe that a caregiver or family member is an impostor, that the patient is living in someone else's home, or that characters on television live in the home. Hallucinations are less common and

tend to be visual in nature. They are often of deceased relatives, with whom the patient may be seen to converse, and often not recognized as hallucinations by the patient.

- **Apathy and indifference.** The most common noncognitive symptoms of AD are apathy and indifference, which can appear in mild AD and worsen as the disease progresses. The signs of apathy include loss of interest in hobbies and family affairs, diminished affection in personal relationships, and decreased initiative in conversation and social interactions.

- **Anxiety.** Anxiety is not uncommon in the moderate and severe stages of AD and can be seen in restlessness, agitation, and repetitive behaviors. AD patients may exhibit separation anxiety when a caregiver has to leave, particularly when the patient is in unfamiliar surroundings.

- **Agitation.** Agitation is a common symptom that occurs in most patients with moderate AD and tends to worsen as the disease progresses. Cursing, screaming, aggression, oppositional behavior, and active resistance to care may occur.

- **Disinhibition.** Disinhibition occurs in about one-third of patients with moderate and severe AD and is characterized by impulsivity and tactlessness.

- **Purposeless activity.** Pacing, wandering, rummaging, picking behaviors (tying and untying knots, unraveling thread, repetitively picking at clothes), and other aberrant

motor activities are prominent in approximately 50% of AD patients and are most common in moderate and severe AD. Wandering in moderate or severe AD is a major concern for caregivers.

- **Sleep disorders.** Sleep disorders seen in AD include confusion upon waking in the middle of the night, insomnia, sleep apnea, and REM behavior disorder, in which patients act out during dreaming and may sleepwalk, grunt, or shout.

- **Aggression and inappropriate sexual behavior.** Aggression and inappropriate sexual behavior are most prominent in moderate and severe AD. Physical aggression is seen in a substantial minority of AD patients and is associated with impairment in activities of daily living, depression, and impaired verbal skills. Inappropriate sexual behavior, mainly unwanted sexual advances, is rare in AD.

- **Delirium.** Patients with AD are at high risk for developing delirium when they are hospitalized. Delirium is an acute medical condition characterized by disorientation, agitation, hallucinations, and fluctuating alertness and attention caused by physical illness or psychological stress.

VI. TREATMENT OF ALZHEIMER'S DISEASE

Experts recommend that the cognitive, or primarily intellectual decline in AD be treated with appropriate medication as soon as the diagnosis is made and up until the terminal stage. Although the improvement seen in cognitive functioning with medication is modest, the quality of life of the patient improves, the patient's decline may be slowed, and institutionalization of the patient may be postponed [16:103]. On the other hand, the noncognitive, or psychiatric and behavioral symptoms of AD, such as hallucinations or agitation, are sometimes provoked by conditions such as hunger or pain that caregivers can alter. Although caregivers can use medications to treat many noncognitive symptoms, experts recommend first looking for and attempting to eliminate external causes of these behaviors. For all symptoms of AD, caregivers can usually make nonpharmacologic interventions that significantly improve the patient's experience and functioning.

Treatment of Cognitive Symptoms of Alzheimer's Disease

The biochemistry of AD is complex and not fully understood. In theory, medical intervention in the disease could happen many different ways by targeting any of the chemical processes involved in AD. While researchers investigate these many potential therapies for AD, physicians are limited to using only two classes of drugs approved by the Federal Drug Administration (FDA) for treating AD. On the other hand, the effectiveness of behavioral and environmental interventions aimed at improving cognition in patients with AD is difficult to evaluate, but studies suggest the more modest nonpharmacologic approaches may be the most effective and easiest to carry out.

Medications for cognitive symptoms of AD. Researchers are investigating many drug therapies that could potentially reduce neuropathology in AD [27:13–15; 69]. For example:

- Inhibitors of either β- or γ-secretase are known to reduce Aβ production and are being studied as treatments for AD.

- Some nonsteroidal anti-inflammatory drugs may selectively lower production of Aβ42, possibly by inhibiting γ-secretase, and are also being studied.

- Cholesterol-lowering drugs called statins appear to decrease Aβ production and deposition and may have potential for treating AD.

- In addition, drugs that may remove Aβ deposits from the brain or prevent Aβ aggregation are being studied.

- Immunization directly with Aβ or passively with Aβ antibodies may someday direct the body's immune system to remove Aβ plaques.

- Zinc appears necessary for Aβ aggregation, and metal chelator drugs that combine with zinc may be useful in inhibiting Aβ aggregation.

- Nerve-growth factor secreted in the brain by patients' own genetically engineered cells may eventually help prevent the loss of neurons in AD.

- Kinase inhibitors that block the hyperphosphorylation of tau that leads to formation of neurofibrillary tangles may also be used to treat AD.

Thus, research is ongoing with many treatment approaches, including studying naturally occurring substances such as tea and curcumin (the yellow pigment in curry spice) [65] that may alter the biological mechanisms responsible for AD.

Only two types of drugs, however, have been approved by the FDA for treatment of AD, and these medications mainly enhance the patient's remaining neurologic functioning rather than slow the disease process. One class of drugs is the acetylcholinesterase inhibitors. The other class consists of one drug, a glutamate receptor blocker.

Early AD researchers knew that acetylcholine, a neurotransmitter in the brain, is deficient in AD patients, as are several other neurotransmitters and that the activity of acetylcholinesterase, an enzyme that breaks down acetylcholine, is high within Aβ plaques. This suggested that degenerating neurons in AD were acetylcholinergic [28:10]. For these and other reasons, acetylcholinesterase inhibitors were the first drugs developed and approved for treating AD. They work by reducing the activity of acetylcholinesterase in the cleft between the two membranes within synapses. One neuron influences another at a synapse when the first neuron's membrane releases a neurotransmitter and the receptors of the second neuron's membrane receive it. The excess neurotransmitter between membranes as well as the neurotransmitter in receptors is quickly broken down by enzymes into smaller molecules that are absorbed by the first neuron and recycled into neurotransmitter. In this way, the activity of the neurotransmit-

ter is regulated by rapidly clearing it from the synaptic cleft. When the activity of acetylcholinesterase is inhibited, acetylcholine remains in the synaptic cleft longer and continues to stimulate receptors in the second neuron.

Four acetylcholinesterase inhibitors have been approved by the FDA. Tarcine (Cognex), the first to be approved, is rarely used because it has many side effects and has to be taken four times a day. The second acetylcholinesterase inhibitor approved was donepezil (Aricept). It was followed by rivastigmine (Excelon) and then galantamine (Reminyl). Excelon, in addition to inhibiting acetylcholinesterase, also inhibits butylcholinesterase, another enzyme that breaks down acetylcholine and that may additionally enhance the toxic effects of Aβ plaques. Reminyl inhibits only acetylcholinesterase but also stimulates neurons to release acetylcholine and other neurotransmitters. Studies have failed to find significant differences in the effectiveness and tolerability of the three newer acetylcholinesterase inhibitors. Side effects common to these drugs include nausea, vomiting, diarrhea, and dizziness, but these can usually be avoided by slowly increasing the dose until the desired maintenance level is reached. All the acetylcholinesterase inhibitors are approved for treating mild and moderate AD [16:92–97].

Research on the effectiveness of acetylcholinesterase inhibitors shows that patients treated with them show a mild but measurable improvement in cognitive functioning after 12 weeks. This improvement includes significant improvement in noncognitive symptoms, such as depression, psychosis, agitation, and wandering, and noticeable improvement in the performance of activities of daily living [40]. These changes are clinically significant: patients in

one study who received acetylcholinesterase inhibitor treatment were able to postpone placement in a nursing home for almost 2 years longer than untreated patients [16:103]. In addition, studies suggest treatment with acetylcholinesterase inhibitors may slow the rate of decline of AD patients and produce beneficial effects even in patients with severe AD. In studies in which acetylcholinesterase inhibitors were discontinued, patients' condition declined over a 6-week period to nearly the level of untreated patients. Stopping medication of some patients can also precipitate a severe cognitive and behavioral decline that cannot be reversed by restarting treatment. Studies of acetylcholinesterase inhibitors strongly support the conclusion that treatment with these drugs should be started as early as possible for every patient with AD and should not be discontinued [16:98–103; 40].

The other class of drugs used to treat of AD is the glutamate receptor blockers, of which only one drug, memantine (Namenda), has been approved. Namenda had previously been approved in Europe for treatment of a variety of neurologic disorders in which it acts as an effective neuroprotective agent, limiting the spread of damage around injured or diseased neurons. Injured neurons release large amounts of the neurotransmitter glutamate. In addition, Aβ accumulations around neurons promote the release of glutamate and inhibit its uptake. Excessive glutamate overstimulates glutamate receptors of healthy neurons, overstressing them and leading to their degeneration, death, and the release of more glutatmate. When Namenda attaches to glutamate receptors, their responsiveness to glutamate is reduced but not eliminated, allowing the receptors to operate relatively normally [45].

The FDA has approved Namenda for the treatment of moderate and severe AD. The drug has relatively few side effects and no significant interactions with other drugs. Patients with moderate and severe AD treated with Namenda show slight but statistically significant improvement in cognitive performance, rate of deterioration, and functional capacity [1]. To date, however, clinical trails of Namenda with patients with mild AD have not been successful. Research and clinical experience suggest that patients treated with Namenda combined with an acetylcholinesterase inhibitor do better than patients treated with either alone [16:104; 40]. As with the acetylcholinesterase inhibitors, Namenda improves the condition of AD patients but does not prevent their eventual decline.

Alternative treatments for cognitive symptoms of AD. Vitamins, herbs, hormones and other medications have been suggested for the treatment of AD. Many of these alternative treatments for AD involve altering modifiable risk factors for the disease and are discussed in the chapter "Causes of AD" under “Other Risk Factors” on page 19.

Of the alternative treatments for AD, only vitamin E, an antioxidant, is recommended by the American Academy of Neurology as a treatment option, primarily because of its tolerability and limited evidence that it may slow the progression of AD. A dosage of 1,000 international units twice a day is recommended [19:1157–1158].

The risk of significant side effects and the absence of demonstrated benefits make the use of other alternative treatments for AD inadvisable [19:1158]. Among these treatments are C and

B vitamins, gingko biloba, huperzine A, selegiline (Eldepril), *Melissa oficinalis* (lemon balm), hydergine, chelation therapy, antibiotics, NSAIDs, estrogen, and statins.

Behavioral interventions for cognitive symptoms of AD. Nonpharmacologic approaches to improving the cognitive functioning of AD patients vary greatly in technique and treatment goal, and studies evaluating these approaches are less rigorous and more difficult to compare than studies of the effects on cognition of medications. In addition, many behavioral treatments devised for research purposes are unavailable to the typical AD patient. A few generalizations can be made about these approaches, however.

First, "global stimulation," such as recreational activity, participation in hobbies, exercise, and social interaction, has been shown to be more effective in improving the functioning of AD patients than "cognitive-specific" interventions, such as memory training or training in specific skills of daily living. Improvements from global stimulation are broad and include improvement in behavioral disturbances, memory, and functional living skills [20].

Second, when cognitive-specific interventions are used, restorative strategies, which largely involve practice and support in practical skills using the patient's existing abilities, are more effective than compensatory strategies, which attempt to teach patients novel techniques such mnemonic systems for compensating for cognitive deficits [67].

Third, behavioral treatments for cognitive symptoms may provoke frustration and depression in patients and caregivers alike if they are not inherently enjoyable and if they disregard

patients' real limitations [68]. Further, the effects of cognitive training may not always be seen in patients' everyday functioning and may not always be lasting [16:105].

Research on specific types of behavioral intervention for cognitive symptoms of AD strongly suggests that some are effective [19:1160]. For example:

- Graded assistance (the least assistance needed by a patient) combined with practice and positive reinforcement improves performance of daily activities.

- Awareness training, scheduled toileting, and prompted voiding reduce urinary incontence.

- Multistrategy group therapies utilizing reality orientation (frequent reorienting of the patient to time, place, season, etc.), remotivation, sensory stimulation, reminiscence, and exercise improve activities of daily living.

- Intensive, long-term education, support, and counseling programs for caregivers can delay nursing home placement by up to 2 years.

Treatment of Noncognitive Symptoms of Alzheimer's Disease

Like the cognitive symptoms of AD, noncognitive symptoms, such as depression or agitation, can be treated either pharmacologically or behaviorally and environmentally. Experts recommend that caregivers always look for ways to manage noncognitive symptoms without the use

of medications. If medications are required, care should be exercised to select drugs that are well tolerated by dementia patients.

Medications for noncognitive symptoms of AD. Suggestions and cautions for treating the following noncognitive symptoms of AD pharmacologically come from both research and clinical experience:

- **Depression.** Although three broad classes of antidepressants are commonly used, only the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac) and paroxetine (Paxil), are recommended as a first-line treatment for AD patients, since these drugs have few, mild adverse effects. Studies of treatment of depression in AD patients with SSRIs have produced conflicting results, but on the whole, SSRIs appear to be of some benefit. Tricyclic antidepressants, such as amitriptyline (Elavil), should be avoided with AD patients, because they have anticholinergic effects (which reduce the activity of acetylcholine in the brain) that exacerbate cognitive symptoms of AD and cause other adverse side effects [16:108–109]. The third class of antidepressants, the monoamine oxidase inhibitors (MAOIs), such as isocarboxazid (Marplan), is also considered inappropriate for treating depression in AD, because of the adverse side effects, drug interactions, and dietary restrictions associated with their use [68].

- **Hallucinations and delusions.** Limited research evidence demonstrates that treatment with acetylcholinesterase inhibitors delays the emergence of psychotic symptoms and reduces existing symptoms. Patients taking acetylcholinesterase inhibitors may still

require antipsychotic medication, however, in which case the newer antipsychotic medications, such as risperidone (Risperdal) and olanzapine (Zyprexa), are clearly preferable over the older antipsychotic medications, such as haloperidol (Haldol©). The older medications, which reduced the activity of the neurotransmitter dopamine, can cause severe adverse reactions in some dementia patients as well as muscle rigidity and tardive dyskinesia (uncontrollable movements of the mouth and tongue), to which the elderly are particularly susceptible. The newer antipsychotic medications have more benign side effects, affect other neurotransmitter systems in addition dopaminegric systems, and may even increase levels of acetylcholine. Clinical experience suggests these medications are useful in treating psychotic symptoms of AD [16:109–110].

- **Sleep disorders.** Common sleep disorders associated with AD include insomnia, daytime sleeping, restless-leg syndrome, REM behavior disorder, and confusion in the middle of the night. If environmental and behavioral interventions for sleep disorders fail to be effective, limited use of medications may be required. Nonprescription sleeping aids, which often contain anticholinergic agents, are generally not recommended for AD patients. Use of the older benzodiazepine drugs, such as diazepam (Valium), is also discouraged because their effects are too long lasting. Trazodone (Desyrel), an older antidepressant, is sometimes used as a sleeping aid but causes a marked increase in daytime confusion in some dementia patients. Sleep medications that are well tolerated by dementia patients include zolpidem (Ambien) for patients who wake up too early, zaleplom (Sonata) for patients who have trouble falling asleep, and clonazepam

(Klonopin) for patients with REM sleep disorder. Treatment with acetylcholinesterase inhibitors usually has a beneficial effect on sleep disturbances in AD as well [16:113–114].

- **Anger and irritability.** Poor sleep quality, depression, and discomfort often lead to anger and irritability. If these and other environmental causes have been ruled out, medications may be tried, including appropriate antidepressants (SSRIs) or one of the newer antipsychotics. The antianxiety drug alprazolam (Xanax) may also be of benefit in treating anger and irritability [16:115].

- **Aggression and inappropriate sexual behavior.** If behavioral strategies are ineffective in curbing angry outbursts, medications can be tried. The newer antipsychotic medications, such as risperidone (Risperdal) and olanzapine (Zyprexa), should be used first because of their mild side effects. If problems with aggression persist, inderal (Propranolol), an antihypertension drug, or valproate (Depakote), an anticonvulsant, can be tried. Both of these medications have sedating effects. Medroxyprogesterone (Provera), a female hormone, can be useful in controlling both aggression and inappropriate sexual behaviors in men [16:115–116].

- **Anxiety, agitation, and repetitive behaviors**. If a physical condition, environmental condition, or emotional concern cannot be identified as causing anxiety in an AD patient, then a medication may be helpful. A sedative or antidepressant (SSRI) may be effective. If anxiety is persistent or unmanageable, a short-acting benzodiazepine anti-

anxiety agent, such as lorazepam (Ativan), may help, as may the longer-acting benzodiazepine alprazolam (Xanax). The nonbenzodiazepine agent buspirone (BuSpar), while having milder side effects than the benzodiazepines, is less effective in controlling anxiety. In addition, treatment with an anticonvulsant medication, such as lamotrigine (Lamictal) or valproate (Depakote), sometimes alleviates anxiety [16:116–117].

- **Epileptic seizures.** Epilepsy and seizures occur in about 10% of AD patients, usually in the moderate or severe stages. Any of a variety of common anticonvulsant medications can usually eliminate seizures in AD patients with few side effects [16:117–118].

Behavioral interventions for noncognitive symptoms of AD. Nonpharmacologic treatment of noncognitive symptoms of AD ranges from practical, common-sense approaches to special treatment techniques developed by clinicians and researchers.

In general, experts recommend looking for causes of behavioral disturbances that AD patients may be unable to communicate [16:107–119]. For example, anger, irritability, anxiety, and agitation may be caused by pain, hunger, undiagnosed physical illness, or other physical discomfort, such as constipation. Loss of sleep or depressed mood can cause or exacerbate anger or irritability. A stressful environment may also lead to disturbances in behavior, as can emotional distress, such as fear of abandonment. Alleviating discomfort, stress, and worry is the first step in reducing irritability and anxiety.

Depression in AD can also be addressed with nonpharmacologic interventions alone or in combination with antidepressant medication. If depression seems related to the diagnosis of AD or to frustration because of deteriorating abilities, family support or participation in a support group consisting of patients or patients and caregivers can help the AD patient express fear, sadness, or anger and better tolerate feelings of loss. Involvement in family activities and engagement in other pleasurable pastimes help give AD patients a sense of control, independence, and being needed. Any measure that improves the patient's quality of life usually helps lessen depression [16:109–109].

Sleep disorders in AD can also be treated without the use of prescription medications, which physicians recommend be used by most people as little as possible. Caregivers can encourage patients to follow the principles of sleep hygiene, practices that promote healthy, restorative nighttime sleeping [16:114]. A list of sleep hygiene principles is shown in Table VI-1.

Patients with AD are also at high risk for developing delirium, a cause of illness and death, when hospitalized. Patients with delirium may be placed in restraints or given potent sedatives. However, acetylcholinesterase inhibitors help prevent delirium [16:119], and behavioral interventions can reduce the risk and severity of delirium. In addition to bringing familiar items from home to help comfort and orient the patient, caregivers can practice delirium-prevention measures [16:119]. Table VI-2 is a list of delirium-prevention measures for the elderly.

Table VI-1:
Principles of Sleep Hygiene[a]

- Make sure the sleeping environment is quiet and restful. Discourage television, as it tends to be arousing. Soft music can be helpful.
- A warm evening bath may help the person to relax.
- Avoid stimulants, such as caffeine, in the evening.
- Limit fluids prior to bedtime and make sure the person has used the restroom.
- If the person wakes too early, try going to bed later.
- Arouse the person at the same time every morning, regardless of how little sleep they may have had the night before.
- Encourage exercise during the day, but avoid it in the evening hours.
- Avoid daytime napping, especially in the early evening.
- Increase natural light exposure during the day.

[a][16:114].

Table VI-2:
Delirium-Prevention Measures[a]

- Have an orientation board with the names of the care team members and the day's schedule visible. Review with the patient.
- Communicate frequently to reorient the patient to date and location.
- Perform a relaxation protocol at bedtime: warm drink, relaxation tape or music, and back massage.
- Reschedule medications and procedures to allow sleep.
- Try to have the patient move as much as possible using range-of-motion exercises. A physical therapist can be helpful in this regard.
- For the hearing impaired, make sure hearing aids are available.
- Have visual aids available for those with visual impairment (such as glasses, fluorescent tape on call bell, and telephone with illuminated keypad).
- Make sure the patient is drinking enough; dehydration can aggravate delirium.

[a][16:119].

In addition to these practical, common-sense recommendations, many other nonpharmacologic therapies for noncognitive symptoms of AD have been devised. It is difficult to judge the effectiveness of these therapies because research on them is rarely replicated and usually uses small samples of patients and weak research designs [44]. A few research findings, however, stand out as fairly reliable and important:

- A few simple interventions consistently have a positive effect on problem behaviors of AD patients: a brightly lit environment reduces aggression, agitation, and other behavioral disturbances; music of the patient's preference reduces agitation, aggression, and mood disturbances, particular when the patient is eating or bathing; and walking and other forms of light exercise reduce wandering, aggression, and agitation [19:1160].

- Most simple psychosocial interventions involving multiple activities, such as music, exercise, crafts, and relaxation, led by trained staff reduce problem behaviors in people with dementia [19:1161].

- Patients in Alzheimer's specialized care units experience less agitation, use of restraints, and catastrophic reactions than patients in nursing homes that are not specialized [19:1161].

- Caregiver education, support, and training used together in comprehensive programs can delay nursing home placement and reduce depression, tension, anger, fatigue, and confusion in caregivers [19:1161].

VII. CONCLUSION: CAREGIVER STRESS

Family caregivers of Alzheimer's patients must cope with a variety of stresses inherent in their special role. Chief among these is coping with the intellectual and behavioral decline of their loved one. Caregivers must make many management decisions pertaining to the patient's welfare as well. For example, caregivers must decide when and how to ask a loved one to give up driving, must guard against the patient's wandering away from home, must arrange for someone to manage the patient's financial affairs, must encourage the patient draw up a will, must obtain durable power of attorney for managing the patient's legal affairs, must often arrange and finance the patient's transition to a nursing facility, and must decide when additional medical care for an end-stage patient will only prolong the process of dying. As AD progresses, a caregiver's burden of responsibilities increases, he or she experiences diminishing emotional support if the patient is a spouse or parent, and more of the his or her time must be spent caregiving. As a result, it is not uncommon for caregivers to experience emotional stress, depression, and social isolation. In fact, studies show that about a third of caregivers of AD patients experience significant levels of depression [16:143–165].

Family caregivers of Alzheimer's patients can take practical steps to protect their own health and remain effective in caregiving. For example, to minimize the stress of caregiving, one expert on AD [16:160–165] recommends that caregivers:

1. Educate themselves about the course of AD and the caregiving demands they can expect.

2. Get medical care (an acetylcholinesterase inhibitor or Namenda or both) for the patient as soon as the diagnosis is made and treat noncognitive symptoms with appropriate medications if necessary.

3. Take care of their own emotional and physical health.

4. Plan ahead for dealing with financial, legal, and nursing home decisions. Early planning allows AD patients to participate.

5. Share the burden of caring for the AD patient with others. Arrange to have time to relax and engage in pleasurable activities.

6. Join a support group or an on-line forum for AD caregivers. Experienced caregivers can offer emotional support, wisdom, and practical suggestions.

Studies of successful caregivers show that they attend to the emotional cues of patients to learn how to prevent difficult behaviors, respond to the needs of patients with flexibility and creativity, educate themselves about AD and practical management strategies, take advantage of supportive resources, involve family and friends in caregiving, and balance the needs of patients with their own needs [54:64]. Thus, quality of life for both patient and caregiver depends upon caregivers' resourcefulness and courage throughout the course of the AD.

APPENDIX A: MINI MENTAL STATUS EXAMINATION

INSTRUCTIONS FOR ADMINISTRATION OF
MINI MENTAL STATUS EXAMINATION[a]

ORIENTATION

1. Ask for the date. Then ask specifically for parts omitted.
i.e., "Can you also tell me what season it is?" One point for each correct.
2. Ask in turn, "Can you tell me the name of this place?", town, county, etc.
One point for each correct.

REGISTRATION

Tell the person you are going to test their memory. Then say the names of three unrelated objects, clearly and slowly, about one second for each. After you have said all three, ask him to repeat them. This first repetition determines his score (0-3) but keep saying them until he can repeat all three, up to six trials. If the subject does not eventually learn all three, recall cannot be meaningfully tested.

ATTENTION AND CALCULATION

Ask the subject to begin with 100 and count backwards by 7. Stop after five subtractions. Score the total number of correct answers.

If the subject cannot or will not perform this task, ask him to spell the word "world" backwards. The score is the number of letters in correct order.
i.e., dlrow = 5 points, dlorw = 3 points.

RECALL

Ask the patient if he can recall the three words you previously asked him to remember. One point for each correctly recalled.

LANGUAGE

Naming: Show the subject a wristwatch and ask her what it is.
Repeat with a pencil. One point for each named correctly.
Repetition: Ask the patient to repeat the sentence after you. Allow only one trial.
3 Stage Command: give the verbal instructions, then present the subject a sheet of paper. One point for each part of the command that is correctly executed.
Reading: Have the subject read the phrase "CLOSE YOUR EYES". The letters should be large and dark enough for the subject to read. Ask him to "Read the sentence and do what it says." Score correctly only if they read and the phrase and close their eyes.
Writing: Give the subject a blank piece of paper and ask her write a sentence for you. Do not dictate a sentence, it is to be written by the subject spontaneously. To score correctly, it must contain a subject and verb and be sensible. It should be a complete thought. Correct grammar and punctuation are NOT necessary.
Copying: On a piece of paper, draw intersecting pentagons, each side about one inch and ask him to copy it exactly as it is. To score correctly, all ten angles must be present AND two must intersect. Tremor and rotation are ignored.

Estimate the subject's level of sensorium along a continuum, from alert to coma.

TOTAL SCORE POSSIBLE = 30
23 OR LESS: HIGH LIKELIHOOD OF DEMENTIA
25-30: NORMAL AGING OR BORDERLINE DEMENTIA

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[a][23]

MINI MENTAL STATUS EXAM

PATEINT'S NAME: _____

Date: _____ Client's Highest Level of Education: _____

Maximum Score Score ORIENTATION

5 ( ) What is the (year) (season) (date) (day) (month)?

5 ( ) where are we: (state) (county) (town) (hospital) (floor)?

REGISTRATION

3 ( ) Name 3 objects: One syllable words, 1 second to say each.
Then ask the patient all 3 after you have said them.

Give 1 point for each correct answer. Then repeat them until he learns all 3.
Count trials and record. Trials _____

ATTENTION AND CALCULATION

5 ( ) Serial 7's. 1 point for each correct. Stop after 5 answers. Alternatively spell "world" backwards.
100 – 93 – 86 – 79 – 72 – 65 – 58

RECALL

3 ( ) Ask for 3 objects repeated above. Give 1 point for each correct.

LANGUAGE

9 ( ) Name a pencil, and watch (2 points)

( ) Repeat the following: "No ifs, ands, or buts." (1 point)

( ) Follow a 3-stage command:
"Take this paper in your right hand,
fold it in half,
and put it on the floor." (3 points)

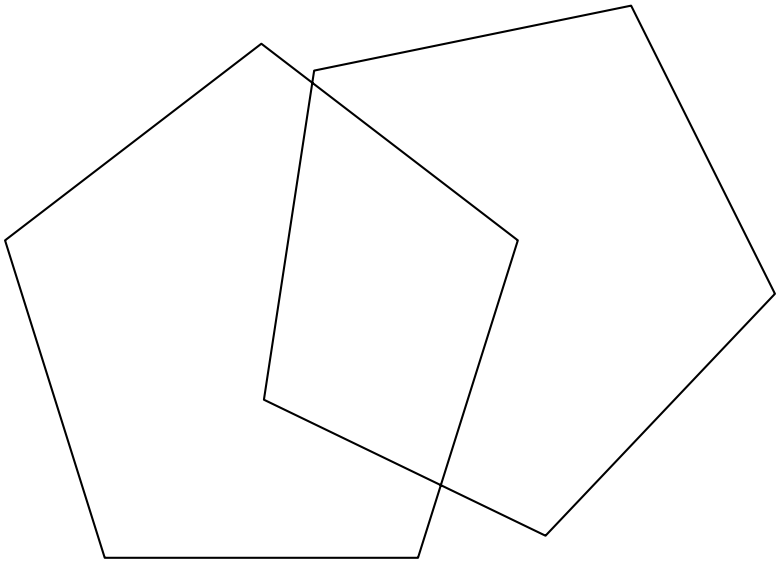
( ) Read and obey the following: "Close your eyes"
(1 point)

( ) Write a sentence. (1 point)

( ) Copy design. (1 point)

_____
Total Score

Assess level of consciousness _____
along a continuum. (Alert) (Drowsy) (Stupor) (Coma)



Close your eyes.

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